FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF DESLORATADINE

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This is to certify that the dissertation entitled**, "FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF DESLORATADINE"** Submitted by **Mr. S.GANESAN** in the Department of Pharmaceutics, Madurai Medical College, Madurai – 20, in partial fulfillment of the requirement for the Degree of **Master of Pharmacy** in **Pharmaceutics**, is a bonafide work carried out by him, under the guidance and supervision of **Prof. Mr.A.Abdul Hasan Sathali**, **M.Pharm.,(Ph.D)** Professor and Head, in the Department of Pharmaceutics, Madurai Medical College, Madurai-20,during the academic year 2011 – 2012.

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I wish him success in all his endeavors.

Place: Madurai

Date: **(Prof. Mr.A.Abdul Hasan Sathali)**

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CHAPTER-I

INTRODUCTION

ORAL DRUG DELIVERY SYSTEM

The oral route of drug administration is the most important method of administration of drug for systemic effect, despite of tremendous advancement in drug delivery system. Its ease of administration, pain avoidance and various advantages over other routes is the reason that the oral route achieved such popularity. But the most evident drawback of oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patient's incompliance particularly in and films) may show greater patient acceptability and convenience.

Fast-dissolving oral delivery systems are solid dosage forms, which disintegrate or dissolve within 1 min when placed in the mouth without drinking of water. After disintegrating in mouth, enhanced the clinical effect of drug through pre-gastric absorption from mouth pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. More recently, Fast-dissolving drug delivery systems have rapidly gained acceptance as an important new way of administering drugs. They are usually used for pharmaceutical and nutraceutical products. It is the newest frontier in drug delivery technology that provides a very convenient means of taking medications and supplements. Fast dissolving drug delivery system are also applicable when local action in the mouth is desirable such as local anesthetic for toothaches, oral ulcers, cold sores, or teething.

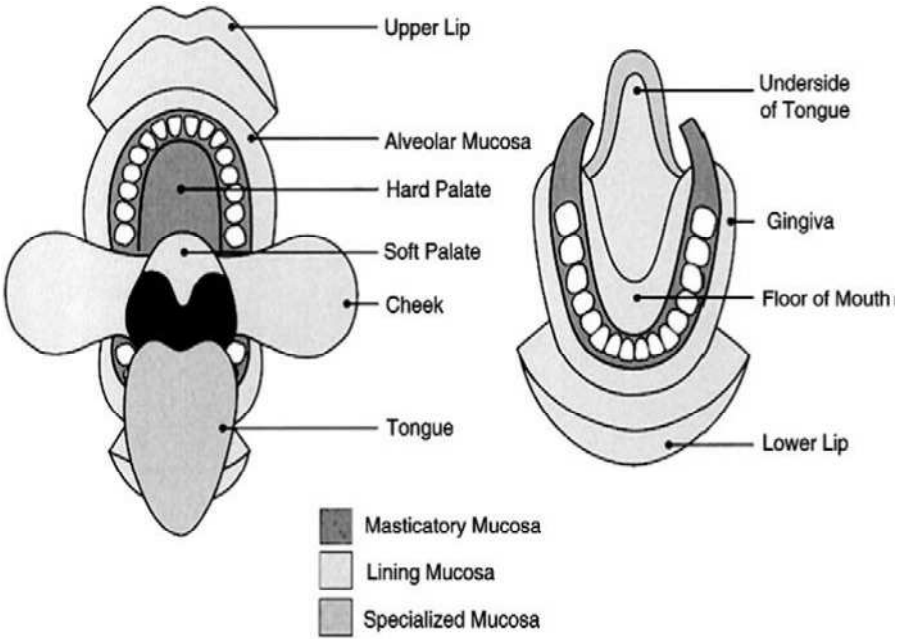
This novel drug delivery system can also be beneficial for meeting the current needs of the industry are improved solubility/stability, biological half-life and bioavailability enhancement of drugs. (Kaur *et al*., 2012)

Overview of Oral Mucosa

The oral cavity comprises the lips, cheek, tongue, hard palate, soft palate and floor of the mouth. The lining of the oral cavity is referred to as the oral mucosa, and includes the buccal, sublingual, gingival, palatal and labial mucosa. The buccal, sublingual and the mucosal tissues at the ventral surface of the tongue account for about 60% of the oral mucosal surface area. The top quarter to one-third of the oral mucosa is made up of closely compacted epithelial cells. The primary function of the oral epithelium is to protect the underlying tissue against potential harmful agents in the oral environment and from fluid loss. Beneath the epithelium are the basement membranes, lamina propia and submucosa. The oral mucosa also contains many sensory receptors including the taste receptors of the tongue. Three types of oral mucosa can be found in the oral cavity; the lining mucosa is found in the outer oral vestibule (the buccal mucosa) and the sublingual region (floor of the mouth). The specialized mucosa is found on the dorsal surface of tongue, while the masticatory mucosa is found on the hard palate (the upper surface of the mouth) and the gingival (gums). The lining mucosa comprises approximately 60%, the masticatory mucosa approximately 25%, and the specialized mucosa approximately 15% of the total surface area of the oral mucosal lining in an adult human. The masticatory mucosa is located in the regions particularly susceptible to the stress and strains resulting from masticatory activity. The superficial cells of the masticatory mucosa are keratinized, and a thick lamina propia tightly binds the mucosa to the underlying periosteum. Lining mucosa on the other hand is

not nearly as subject to masticatory loads and consequently, has a non-keratinized epithelium, which sits on a thin and elastic lamina propia and a sub mucosa. The mucosa of the dorsum of the tongue is a specialized gustatory mucosa, which has well papillated surfaces which are both keratinized and some non-keratinized.

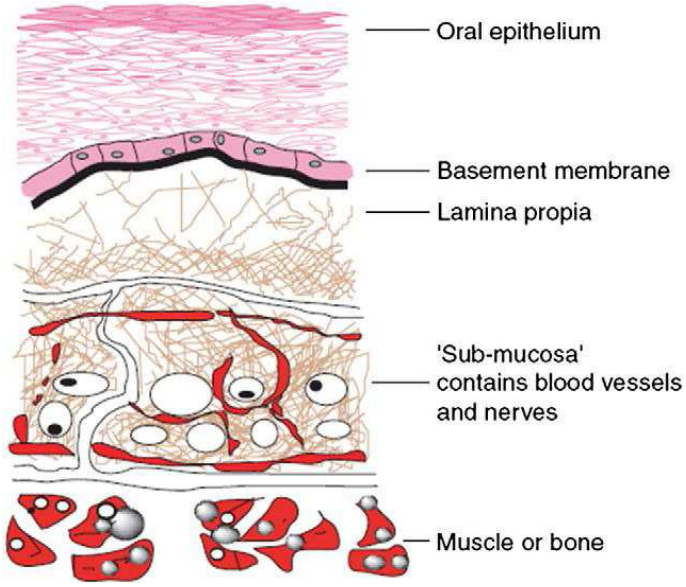
Schematic representation of the different linings of mucosa in mouth



ORALLY DISINTEGRATING DOSAGE FORMS

The concept of orally disintegrating dosage forms has emerged from the desire to provide patients with more conventional means of taking their medication. Interestingly, the demand for ODDFs has enormously increased during the last decade, particularly for geriatric and pediatric patients who experience difficulty in swallowing conventional tablets and capsules. Hence, they do not comply with prescription, which results in high in33cidence of ineffective therapy.

Schematic diagram of buccal mucosa



The advantages and disadvantages associated with utilizing the oral mucosa as a drug delivery site

Advantages	Disadvantages
Accessible	Permeability barrier of oral mucosa
Self-administrable	Saliva washes away the drug
Oral mucosa repairs rapidly	Mastication and speech may dislodged
Different areas of the oral cavity have different permeability characteristics	Delivery device
Highly hydrated environment to dissolve drug	Requires formulation for agreeable taste

Sustained delivery possible	Highly enzymatic environment
Potential reduction of systemic side effects	Relatively small surface area
Avoid the hepatic first pass effect	Risk of choking on or swallowing delivery device

In disease conditions such as motion sickness, sudden episodes of attacks of coughing and repeated emesis swallowing conventional solid dosage forms become difficult. Orally disintegrating dosage forms can serve as an effective alternative mode of drug delivery in such situations. When put in the mouth, these dosage forms disintegrate instantly to release the drug, which dissolves or disperses in the saliva. Thereafter, the drug may get absorbed from the pharynx and esophagus or from other sections of GIT as the saliva travels down. In such cases, bioavailability is significantly greater than that observed from conventional tablet dosage form.

The novel technology of oral disintegrating dosage forms is known as fast dissolve, rapid dissolve, rapid melt and quick dispersible tablets (Gupta *et al*, 2010). However, the function and concept of all these dosage forms are similar.

Different orally disintegrating dosage forms are as follows:

1. *Orally disintegrating tablets:*

It is a tablet that dissolves or disintegrates in the oral cavity without the need of water or chewing.

2. *Fast dissolving films:*

The fear of taking solid tablets and the risk of choking for certain patient population still exists despite their short dissolution and disintegration time. It consists of very thin oral strip,

which releases the active ingredient immediately after uptake in to the oral cavity. It combines all advantages of tablets along with liquid dosage forms. This system is simply placed on patients tongue or any other mucosal surface, instantly wet by saliva; film rapidly hydrates and dissolves to release the medication.

3. ***Fast Caps:***

A new type of fast disintegrating drug delivery system based on gelatin capsules was developed. In contrast to conventional hard gelatin capsules, the fast caps consist of gelation of low bloom strength and various additives to improve the mechanical and dissolution properties of capsule shell. It includes several advantages like high drug loading, possible solid and liquid filling, and no compression of coated taste masked or extended release drug particles / pellets, good mechanical properties, simple manufacturing, mechanical stability and requirement of special packaging.

4. ***Medicated chewing gums:***

It is an attractive alternative for drug delivery system with several advantages including convenience for administration, mainly chewing gum is used to promising controlled release drug delivery system. These are mainly available currently for pain relief, smoking cessation, travel illness and freshening of breath.

5. ***Freeze-dried wafer:***

It is a quick-disintegrating, thin matrix that contains a medicinal agent that does not need water for swallowing. This fragile dosage form requires unit-dose packaging to ensure physical stability. The wafer disintegrates instantaneously in the oral cavity and releases drug, which dissolves or disperses in the saliva. The saliva is swallowed and the drug is absorbed across the gastrointestinal tract (GIT). (Priyanka Nagar *et al*., 2011)

CHAPTER-II

FAST DISSOLVING TABLET - A REVIEW

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance. Also solid oral delivery systems do not require sterile conditions and are therefore, less expensive to manufacture. Patient compliance, high-precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. Excipients and equipments choices will be significantly affected should solid dosage form technologies change in response to the unprecedented shifts in the drug discovery such as genomics. Should next generation drugs are predominantly protein or peptide based, tablets may no longer be the dominant format give the difficulty of dosing such moiety. Injections generally are not favored for use by patients unless facilitated by sophisticated auto injectors. Inhalation is one good alternative system to deliver these drugs, but the increased research into biopharmaceuticals so far has generate predominantly chemical entities with low molecular weights. The development of enhanced oral protein delivery technology by Fast dissolving Tablets which may release these drugs in the mouth are very promising for the delivery of high molecular weight protein and peptide . The oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, manufacturing and ease of administration lead to high levels of patient compliance. (Rajeshree Panigrahi *et al*., 2010)

The problem of swallowing is common phenomenon in geriatric patient due to fear of choking, hand tremors, dysphasia and in young individuals due to underdeveloped muscular and nervous systems and in schizophrenic patients which leads to poor patient

compliance. Difficulties in swallowing of tablet and capsule are also occurring when water is not available, in diarrhea, coughing during the common cold, allergic condition and bronchial infection. Approximately one-third of the population (mainly pediatric and geriatric) has swallowing difficulties, resulting in poor compliance with oral tablet drug therapy which leads to reduced overall therapy effectiveness. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention (Md.Nehal Siddiqui *et al*., 2010).

United States Food and drug administration (FDA) defined fast dissolving tablet (FDT) as "a solid dosage form containing medicinal substance or active ingredient which disintegrate rapidly usually within a matter of seconds when placed upon the tongue." European pharmacopoeia has used the term "Orodispersible tablet" for tablets that disperses readily and within 3 min in mouth before swallowing.(Johnny Edward Aguilar-Diaz *et al*., 2012)

DESIRED CHARACTERISTICS OF FAST DISSOLVING TABLETS

Because administration of FDTs is different from administration of conventional tablets, the FDTs should maintain several unique properties, as listed below (V.Dinesh kumar *et al*., 2011).

Fast Disintegration

FDTs should disintegrate in the mouth without additional water or with a very small amount (e.g., 1–2 ml) of water. The disintegration fluid is provided by the saliva of the patient. The disintegrated tablet should become a soft paste or liquid suspension, which can provide good mouth feel and smooth swallowing. The "fast disintegration" usually means disintegration of tablets in less than 1 minute, but it is preferred to have disintegration as soon as possible.

Taste of Active Ingredients

Because FDTs dissolve or disintegrate in the patient's mouth, the drug will be partially dissolved in close proximity to the taste buds. After swallowing, there should be minimal or no residue in the mouth. A pleasant taste inside the mouth becomes critical for patient acceptance. An ideal taste-masking technology should provide drugs without grittiness and with good mouth feel. The amount of taste masking materials used in the dosage forms should be kept low to avoid excessive increase in tablet size. The taste-masking technology should also be compatible with FDT formulations.

Drug Properties

For the ideal FDT technology, the drug properties should not significantly affect the tablet property. Many drug properties could potentially affect the performance of FDTs. For example, the solubility, crystal morphology, particle size, hygroscopicity, compressibility, and bulk density of a drug can significantly affect the final tablets characteristics, such as tablet strength and disintegration. The FDT technology should be versatile enough to accommodate unique properties of each drug.

Tablet Strength and Porosity

Because FDTs are designed to have a quick dissolution/disintegration time, the tablet porosity is usually maximized to ensure fast water absorption into the tablets. The key properties of the tablets are fast absorption or wetting of water into the tablets and disintegration of associated particles into individual components for fast dissolution. This requires that excipients should have high wettability, and the tablet structure should also have a highly porous network. Because the strength of a tablet is related to compression pressure, and porosity is inversely related to compression pressure, it is important to find the porosity that allows fast water absorption while maintaining high mechanical strength. In addition, low compression pressure causes fast dissolving dosage forms to be soft,

friable, and unsuitable for packaging in conventional blisters or bottles. A strategy to increase tablet mechanical strength without sacrificing tablet porosity or requiring a special packaging to handle fragile tablets should be provided.

Moisture Sensitivity

FDTs should have low sensitivity to humidity. This problem can be especially challenging because many highly water soluble excipients are used in formulation to enhance fast dissolving properties as well as to create good mouth feel. Those highly water-soluble excipients are susceptible to moisture; some will even deliquesce at high humidity. A good package design or other strategy should be created to protect FDTs from various environmental conditions.

Ion Exchange Resin

One of the popular approaches in the taste masking of bitter drugs is based on IER. IER are solid and suitably insoluble high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with the surrounding medium.Being high molecular weight water insoluble polymers, the resins are not absorbed by the body and are therefore inert. The long-term safety of IER, even while ingesting large doses as in the use of cholestyramine to reduce cholesterol is an established unique advantage of IER due to the fixed positively or negatively charged functional groups attached to water insoluble polymer backbone. These groups have an affinity for oppositely charged counter ions, thus absorbing the ions into the polymer matrix. Since most drugs possess ionic sites in their molecule, the resin's charge provides a means to loosely bind such drugs and this complex prevents the drug release in the saliva, thus resulting in taste masking. For taste masking purpose weak cation exchange or weak anion exchange resins are used, depending on the nature of drug. The nature of the drug resin complex formed is such that the average pH of 6.7 and cation concentration of about 40meq/L in the saliva are not able to break the drug

resin complex but it is weak enough to break down by hydrochloric acid present in the stomach. Thus the drug resin complex is absolutely tasteless with no after taste, and at the same time, its bioavailability is not affected.

Classification of IER

IERs contain positively or negatively charged sites and are accordingly classified as either cation or anion exchanger. The functional group in cation exchanger and anion exchanger undergoes reaction with the cations and anions of the surrounding solution respectively. The strong cation exchanger contains sulphuric acid sites whereas weak cation exchangers are based on carboxylic acid moieties. The strong anion exchange resins have quaternary amine ionic sites attached to the matrix, whereas weak anion exchanger has predominantly tertiary amine substituents. Detail of IERs is available which are summarized in Table.

TABLE: EXAMPLES OF IER – DRUG COMPLEX

Resin			Medicament
Name	**Functionality**	**Polymer backbone**	
Amberlite™ IRP64	Weak acid COO^-	Crosslinked polyacrylic	Dextromethorphan, Dimenhydrinate
Amberlite™ IRP69	Strong acid SO^{3-}	Styrene-Divinyl Benzene	Ranitidine
Amberlite™ IRP88	Weak acid COO^-	Crosslinked polyacrylic	Talampacillin-HCl, Paroxetine
Indion 204	Weak acid COO^-	Crosslinked polyacrylic	Norfloxacin, Ofloxacin
Indion 214	Weak acid COO^-	Crosslinked polyacrylic	Azithromycin
Indion 234	Weak acid COO^-	Crosslinked polyacrylic	Ciprofloxacin, Chloroquin phosphate
Kyron T-104	Weak acid COO^-	Crosslinked polyacrylic	Cefpodoxime proxetil
Kyron T-114	Weak acid COO^-	Crosslinked polyacrylic	Ofloxacin
Kyron T-134	Weak acid COO^-	Crosslinked polyacrylic	Metronidazole

Properties of IER

a) Particle size

Decreasing the size of the resin particles significantly decreases the time required for the reaction to reach equilibrium with the surrounding medium; hence larger particle size affords a slower release pattern.

b) Porosity

The limiting size of the ions, which can penetrate into a resin matrix, depends strongly on the porosity. The porosity depends upon the amount of cross-linking substance used in

Polymerization method. The amount of swelling is directly proportional to the number of hydrophilic functional groups attached to the polymer matrix and is inversely proportional to the degree of DVB cross linking present in the resin.

c) Cross-linking

The percentage of cross-linking affects the physical structure of the resin particles. Resins with low degree of cross-linking can take up large quantity of water and swell into a structure that is soft and gelatinous. However resins with high (Divinylbenzene) DVB content swell very little and are hard and brittle.

d) Exchange capacity

The exchange capacity refers to the number of ionic sites per unit weight or volume (mEq. Per gram or meq per ml). The weight basis values (mEq. per gm) is much higher than the volume based exchange capacity since the wet resin is highly hydrated. The exchange may limit the amount of drug that may be adsorbed on a resin, hence affect potency of the complex. Carboxylic acid resins derived from acrylic acid polymers have higher exchange capacities (10meq. /gm) than sulfonic acid (about 4meq. / gm) or amine resins because of bulkier ionic substituents and the polystyrene matrix. Therefore, higher drug percentages may often be achieved with carboxylic acid resins.

e) Acid base strength

It depends on various ionogenic groups incorporated into resins. Resins containing sulphonic, phosphonic or carboxylic acid exchange groups have approximate pKa values of <1, 2, 3 and 4-6 respectively. Anionic exchangers are quaternary, tertiary or secondary ammonium groups having pKa values of >13, 7-9 or 5-9 respectively. The pKa values of resin will have significant influence on the rate at which the drug will be released in the gastric fluid.

f) Selectivity of resin for counter ion

Since IER involves electrostatic forces, selectivity mainly depends on relative charge and ionic radius of hydrated ions competing for an exchange site and to some extent on hydrophobicity of competitor ion.

Salient Features of Fast Dissolving Drug Delivery System

- Ease of administration to patients who refuse to swallow a tablet, such as paediatric and geriatric patients and, psychiatric patients.
- Convenience of administration and accurate dosing as compared to liquids.
- No need of water to swallow the dosage from, which is highly convenient feature for patients who are traveling and do not have immediate access to water.
- Good mouth feels properly of MDDS helps to change the basic view of medication as "bitter pill", particularly for pediatric patients.
- Rapid dissolution of drug and absorption which may produce rapid, onset of action.
- Some drugs are absorbed from the month pharynx and oesophagus as the saliva passes down into the stomach, in such cases bioavailability of drugs is increased.
- Ability to provide advantages of liquid medication in the form of solid preparation. (Bhupendra G Prajapadti *et al*., 2009).

Requirements of Fast Dissolving Tablets

An ideal FDT should

- Have a pleasing mouth feel.
- Require no water for oral administration, yet dissolve / disperse/ disintegrate in mouth in a matter of seconds.
- Have an acceptable taste masking property.
- Be harder and less friable
- Exhibit low sensitivity to environmental conditions (temperature and humidity).

- Allow the manufacture of tablet using conventional processing and packaging Equipments. (Bhupendra G Prajapadti *et al*., 2009).

Advantages of ODTs

1. ODT can be administer to the patients who cannot swallow tablets/cap., such as the elderly, stroke victims, bedridden patients, patients with esophageal problems & patients who refuse to swallow such as pediatric, geriatric & psychiatric patients and thus improves patient compliance .
2. It contain the certain studies which concluded increased bioavailability and proved rapid absorption of drugs through pregastric absorption of drugs from mouth, pharynx & esophagus as saliva passes down .
3. ODT is most convenient for disabled, bedridden patients, travelers and busy people, who do not always have access to water.
4. Good mouth feel property of ODT helps to change the perception of medication.
5. As bitter pill particularly in pediatric patients.
6. The risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.
7. ODT opened new business opportunity like product differentiation, product promotion, patent extension and life cycle management.
8. Suitable during traveling where water may not be available.
9. No specific packaging required can be packaged in push through blisters.
10. Conventional manufacturing equipment.
11. Cost effective.
12. Good chemical stability as conventional oral solid dosage form.

13. New business opportunity like product differentiation, product promotion, patent extension and life style management.
14. Allow high drug loading.
15. Provides rapid drug delivery from dosage forms.
16. Provide advantage of liquid medication in form of solid Preparation.
17. Rapid drug therapy intervention.
18. No chewing needed.
19. Adaptable and amenable to existing processing and packaging Machinery.
20. Rapid onset of action.

Disadvantages of ODTs

1. ODT is hygroscopic in nature so must be keep in dry place.
2. Some time it possesses mouth feeling.
3. It is also shows the fragile, effervescence granules property.
4. ODT requires special packaging for properly stabilization & safety of stable product. (Priyanka Nagar *et al*., 2011)

SELECTION OF FDT DRUG CANDIDATES:

Several factors must be considered when selecting drug candidates for delivery as FDT dosage forms.

- The drugs which have significantly different pharmacokinetic profiles compared with the same dose administered in a conventional dosage. E.g. selegiline, apomorphine, buspirone etc.
- The drugs that produce a significant amount of toxic metabolites mediated by first pass liver metabolism and gastric metabolism and for drugs that have a substantial fraction of absorption in the oral cavity and segments of the pre-gastric GIT.

- Drugs having ability to diffuse and partition into the epithelium of the upper GIT (log P > 1, or preferable > 2); and those able to permeate oral mucosal tissue are considered ideal for FDT formulations.
- Patients who concurrently take anticholinergic medications may not be the best candidates for these drugs.
- Patients with Sjögren's syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for FDT formulations.
- Drugs with a short half-life and frequent dosing.
- Drugs which are very bitter or otherwise unacceptable taste because taste masking cannot be achieved.
- Drugs which require controlled or sustained release are unsuitable candidates of fast dissolving oral dosage forms.
- Pharmaceutical Companies have formulated FDT for various categories of drugs such as neuroleptics, cardiovascular agents, analgesics, antiallergic, antiepileptics, anxiolytics, sedatives, hypnotics, diuretics, anti-parkinsonism agents, anti-bacterial agents and drugs used for erectile dysfunction (Md.Nehal Siddiqui *et al*., 2010).

MECHANISMS OF ODTs

ODTs involve the following mechanisms to achieve the desired fast dissolving characteristics

1. Water must quickly enter into the tablet matrix to cause rapid disintegration and instantaneous dissolution of the tablet.

2. Incorporation of an appropriate disintegrating agent or highly water soluble excipients in the tablet formulation.

3. There are some under mentioned mechanisms by which the tablet is broken down into the smaller particles and then subsequently result a solution or suspension of the drug. (Susijit Sahoo *et al*., 2010)

The mechanisms are-

- High swellability of disintegration
- Chemical reaction
- Capillary action.

Challenges in Formulating ODTS

Palatability

As most drugs are unpalatable, orally disintegrating drug delivery systems usually contain the medicament in a taste-masked form. Delivery systems disintegrate or dissolve in patient's oral cavity, thus releasing the active ingredients which come in contact with the taste buds; hence, taste-masking of the drugs becomes critical to patient compliance.

Mechanical strength

In order to allow ODTs to disintegrate in the oral cavity, they are made of either very porous and soft-molded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, difficult to handle, and often requiring specialized peel-off blister packing that may add to the cost.

Hygroscopicity

Several orally disintegrating dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which calls for specialized product packaging.

Amount of drug

The application of technologies used for ODTs is limited by the amount of drug that can be incorporated into each unit dose. For lyophilized dosage forms, the drug dose

must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs. This parameter is particularly challenging when formulating a fast-dissolving oral films or wafers.

Aqueous solubility

Water-soluble drugs pose various formulation challenges because they form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process. Such collapse sometimes can be revented by using various matrix-forming excipients such as mannitol than can induce crystallinity and hence, impart rigidity to the amorphous composite.

Size of tablet

The degree of ease when taking a tablet depends on its size. It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was one larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve.

Rapid disintegration

MDT is required to disintegrate rapidly in matter of seconds.

Taste and mouth feel characteristics

Approved sweeteners and flavours are typically included to achieve a palatable formulation, but additional taste masking strategies may also be required such as ion exchange resin and active pharmaceutical ingredient encapsulation.

Avoid increase in size

The tablet size of the MDT need to be monitored and is kept small to maintain the characteristic of rapid disintegration.

Good package design

Packing requirements need to be considered early in the development process to protect MDTs from moisture and other environmental hazards (Jaysuhk J Hirani *et al*., 2009).

EXCIPIENTS COMMONLY USED FOR FDT PREPARATION

It contains an active principle, mixture of excipients comprising atleast one disintegrant, a diluents and optionally a swelling agent, a permeabilizing agent, sweeteners and flavourings.

The ingredients used are of food grade and helps to impart desired organoleptic properties and product efficacy (Deshmukh Keshav Ram *et al*., 2011).

Superdisintegrants

The basic approach in FDTs is use of disintegrant. Disintegrant play an important role in the disintegration and dissolution of FDT. It is essential to choose a suitable disintegrant, in an optimum concentration, so as to ensure quick disintegration and high dissolution rates.

Superdisintegrant provide quick disintegration due to combined effect of swelling and water absorption by the formulation. Due to swelling of superdintegrant, the wetted surface of the carrier increases; thus promotes the wettability and dispersibility of the system, thus enhancing the disintegration and dissolution. (Siraj Shaikh *et al*., 2010).

The optimization of tablet disintegration as commonly done by mean of the disintegration critical concentration .Below this concentration the tablet disintegration time is inversely proportional to the disintegrant concentration. Above the critical concentration, the disintegration time remains approximately constant or even increased (Amol V.Patil *et al*., 2011).

Example of some superdintegrants:

- Croscarmellose sodium (Vivasol, Ac-Di-Sol)
- Crospovidone (Polyplasdone)
- Carmellose(NS-300)
- Sodium starch glycolate(SSG)
- Indion-414
- Low substituted Hydroxy propyl cellulose.

Binders

Proper selection of a binder or combination of binder is essential to maintain integrity and stability of the tablet and to achieve desired sensory and melting characteristics. Binding agent may be liquid**,** semi-solid and slid or mixtures of varying molecules weights. (Desmukh Keshav Ram *et al*., 2011)

E.g. cellulosic polymers, povidones, polyvinyl alcohols and acrylic polymers.

Bulking agents

It improves the textural characteristics that in turn enhance disintegration in mouth. Recommended bulking agents for this delivery system should be more sugar – based such as mannitol, lactitol and starch hydrolysate for higher aqueous solubility and good sensory perception. Bulking agents are added in the range of 10 % to about 90% by weight of the final composition. (Desmukh Keshav Ram *et al*., 2011)

Lubricants

It assists in making tablets palatable and provides quicker disintegration. It removes grittiness and assists in drug transport mechanism from mouth down to stomach.

Flavours and sweeteners

Flavours and taste masking agents make the products more palatable and pleasing for patients. The addition of these ingredients assists in overcoming bitterness and

undesirable tablets of some active ingredients. Both neutral and synthetic flavors can be used to improve the organoleptic characteristics of FDTs.

Eg: Dextrose, fructose, aspartame, sodium saccharin, sugar alcohols and sucralose.

METHODOLOGY EMPLOYED FOR FAST DISSOLVING FORMULATIONS

1. Melt granulation

Melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by a meltable binder. The advantage of this technique compared to a conventional granulation is that no water or organic solvents is needed. Because there is no drying step, the process is less time consuming and uses less energy than wet granulation. It is a useful technique to enhance the dissolution rate of poorly water-soluble drugs, such as griseofulvin. This approach to prepare FDT with sufficient mechanical integrity, involves the use of a hydrophilic waxy binder (Superpolystate, PEG - 6 - stearate).

2. Phase transition process

It is concluded that a combination of low and high melting point sugar alcohols, as well as a phase transition in the manufacturing process, are important for making FDTs without any special apparatus. FDT were produced by compressing powder containing erythritol (melting point: 122 °C) and xylitol (melting point: 93 95 °C), and then heating at about 93 °C for 15 min. After heating, the median pore size of the tablets was increased and tablet hardness was also increased. The increase of tablet hardness with heating and storage did not depend on the crystal state of the lower melting point sugar alcohol.

3. Sublimation

In this method a subliming material like camphor, is removed by sublimation from compressed tablets and high porosity is achieved due to the formation of many pores where camphor particles previously existed in the compressed tablets prior to sublimation

of the camphor. A high porosity was achieved due to the formation of many pores where camphor particles previously existed in the compressed Mannitol tablets prior to sublimation of the camphor. These compressed tablets which have high porosity (approximately 30%) rapidly dissolved within 15 seconds in saliva. Granules containing nimesulide, camphor, Crospovidone, and lactose were prepared by wet granulation technique. Camphor was sublimed from the dried granules by vacuum exposure. Conventional methods like dry granulation, wet granulation and direct compression with highly soluble excipients, superdisintegrants and/or effervescent systems can also be used.

4. Three-dimensional Printing (3DP)

Three-dimensional printing (3DP) is a rapid prototyping (RP) technology. Prototyping involves constructing specific layers that uses powder processing and liquid binding materials. A novel fast dissolving drug delivery device (DDD) with loose powders in it was fabricated using the three dimensional printing (3DP) process. Based on computer-aided design models, the DDD containing the drug acetaminophen were prepared automatically by 3DP system. It was found that rapidly disintegrating oral tablets with proper hardness can be prepared using TAG. The rapid disintegration of the TAG tablets seemed due to the rapid water penetration into the tablet resulting from the large pore size and large overall pore volume.

5. Mass Extrusion

This technology involves softening of the active blend using the solvent mixture of water soluble polyethylene glycol and methanol and expulsion of softened mass through the extruder or syringe to get a cylindrical shaped extrude which are finally cut into even segments using heated blade to form tablets. This process can also be used to coat granules of bitter drugs to mask their taste.

6. Spray Drying

In this technique, gelatin can be used as a supporting agent and as a matrix, Mannitol as a bulking agent and sodium starch glycolate or Croscarmellose or Crospovidone are used as superdisintegrants. Tablets manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium. The formulation contained bulking agent like Mannitol and lactose, a superdisintegrant like sodium starch glycolate & Croscarmellose sodium and acidic ingredient (citric acid) and/or alkaline ingredients (e.g. sodium bicarbonate). This spray-dried powder, which compressed into tablets showed rapid disintegration and enhanced dissolution. Maximum drug release and minimum disintegration time were observed with Kollidon CL excipient base as compared to tablets prepared by direct compression, showing the superiority of the spray dried excipient base technique over direct compression technique.

7. Cotton Candy Process

The Shearform technology is employed in the preparation of a matrix known as 'floss', made from a combination of excipients, either alone or with drugs. The floss is a fibrous material similar to cotton-candy fibers, commonly made of saccharides such as sucrose, dextrose, lactose and fructose at temperatures ranging between 180–266 °F. However, other polysaccharides such as polymaltodextrins and polydextrose can be transformed into fibers at 30–40% lower temperature than sucrose. This modification permits the safe incorporation of thermolabile drugs into the formulation. The tablets manufactured by this process are highly porous in nature and offer very pleasant mouth feel due to fast solubilization of sugars in presence of saliva. The manufacturing process can be divided into four steps as detailed below.

a) Floss Blend

In this step, 80% sucrose in combination with mannitol/dextrose and 1% surfactant is blended to form the floss mix. The surfactant acts as a crystallization enhancer in maintaining the structural integrity of the floss fibers. It also helps in the conversion of amorphous sugar into crystalline form from an outer portion of amorphous sugar mass and subsequently converting the remaining portion of the mass to complete crystalline structure. This process helps to retain the dispersed drug in the matrix, thereby minimizing migration out of the mixture.

b) Floss Processing

The floss formation machine uses flash heat and flash flow processes to produce matrix from the carrier material. The machine is similar to that used in 'cotton-candy' formation which consists of a spinning head and heating elements. In the flash heat process, the heat induces an internal flow condition of the carrier material. This is followed by its exit through the spinning head (2000–3600 rpm) that flings the floss under centrifugal force and draws into long and thin floss fibers, which are usually amorphous in nature.

c) Floss Chopping and Conditioning

This step involves the conversion of fibers into smaller particles in a high shear mixer granulator. The conditioning is performed by partial crystallization through an ethanol treatment (1%) which is sprayed onto the floss and subsequently evaporated to impart improved flow and cohesive properties to the floss.

d) Blending and Compression

Finally, the chopped and conditioned floss fibers are blended with the drug along with other required excipients and compressed into tablets. In order to improve the mechanical strength of the tablets, a curing step is also carried out which involves the

exposure of the dosage forms to elevated temperature and humidity conditions, (40 °C and 85% RH for 15 min). This is expected to cause crystallization of the floss material that results in binding and bridging to improve the structural strength of the dosage form.

8. Tablet Molding

Molding process is of two type's i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in molded plates to form a wetted mass (compression molding). The solvent is then removed by air-drying. The tablets manufactured in this manner are less compact than compressed tablets and possess a porous structure that hastens dissolution. The heat molding process involves preparation of a suspension that contains a drug, agar and sugar (e.g. mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30°c.

9. Lyophilization or Freeze-Drying

Freeze drying is the process in which water is sublimed from the product after it is frozen. This technique creates an amorphous porous structure that can dissolve rapidly. A typical procedure involved in the manufacturing of ODT using this technique is mentioned here. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is done by weight and poured in the walls of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying. After freeze-drying the aluminum foil backing is applied on a blister-sealing machine. Finally the blisters are packaged and shipped. The freeze-drying technique has demonstrated improved absorption and increase in bioavailability. The major disadvantages of lyophillization technique are that it is expensive and time consuming;

fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions.

10. Direct Compression

Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied to preparation of ODT because of the availability of improved excipients especially superdisintegrants and sugar based excipients.

a) Superdisintegrants:

In many orally disintegrating tablet technologies based on direct compression, the addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration. For the success of fast dissolving tablet, the tablet having quick dissolving property which is achieved by using the super disintegrants,

b) Sugar Based Excipients:

This is another approach to manufacture ODT by direct compression. The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, and hence impart taste masking property and a pleasing mouthfeel.

11. Nanonization

Nanonization involves reduction in the particle size of drug to nanosize by milling the drug using a proprietary wet-milling technique. The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into MDTs. This technique is especially advantageous for poor water soluble drugs. (A. Gupta *et al*., 2010).

PATENTED TECHNOLOGIES

Zydus technology:

This technology includes physical trapping of the drug in a matrix composed of a saccharide and a polymer. Polymers generally employed are partially hydrolyzed gelatin, hydrolyzed dextran, dextrin, alginates, polyvinyl alcohol, polyvinyl pyrrolidine, acacia, and these mixtures. The methodology involves solution or dispersion of components prepared and filled in to blister cavities, which are frozen in a liquid nitrogen environment. The frozen solvent is removed or sublimed to produce porous wafers.

Lyoc:

Lyoc technology is patented by PHARMALYOC. Oil in water emulsion is prepared and placed directly into blister cavities followed by freeze-drying. Non-homogeneity during freeze-drying is avoided by incorporating inert filler to increase the viscosity finally the sedimentation. High proportion of filler reduces porosity of tablets due to which disintegration is lowered.

Quick solv:

This technology is patented by Janssen Pharmaceuticals. It utilizes two solvents in formulating a matrix, which disintegrates instantly. Methodology includes dissolving matrix components in water and the solution or dispersion is frozen. Then dry the matrix by removing water using an excess of alcohol (solvent extraction). Thus the product formed has uniform porosity and adequate strength for handling.

Nanocrystal technology:

This is patented by Elan, King of Prussia. Nanocrystal technology includes lyophilization of colloidal dispersions of drug substance and water-soluble ingredients filled in to blister pockets. This method avoids manufacturing process such as granulation, blending, and tabletting, which is more advantageous for highly potent and hazardous

drugs. As manufacturing losses are negligible, this process is useful for small quantities of drug.

Flashtab technology:

This is patented by Ethypharm France. This technology includes granulation of excipients by wet or dry granulation method and followed by compressing into tablets. Excipients used in this technology are of two types. Disintegrating agents include reticulated polyvinylpyrrolidine or carboxy methylcellulose. Swelling agents include carboxy methylcellulose, starch, modified starch, microcrystalline cellulose, carboxy methylated starch, etc. These tablets have satisfactory physical resistance. Disintegration time is within 1 min.

Orasolv technology:

This technology is patented by CIMA Labs. This includes use of effervescent disintegrating agents compressed with low pressure to produce the MDTs. The evolution of carbon dioxide from the tablet produces fizzing sensation, which is a positive organoleptic property. Concentration of effervescent mixture usually employed is 20-25% of tablet weight. As tablets are prepared at low compression force, they are soft and fragile in nature. This initiated to develop Paksolv, a special packaging to protect tablets from breaking during storage and transport. Paksolv is a dome-shaped blister package, which prevents vertical movement of tablet within the depression. Paksolv offers moisture, light, and child resistance packing.

Durasolv technology:

This technology is patented by CIMA Labs. The tablets produced by this technology utilize the conventional tableting equipment. Tablets in this are formulated by using drug, nondirect compression fillers, and lubricants. Nondirect compressible fillers are dextrose, mannitol, sorbitol, lactose, and sucrose, which have advantage of quick

dissolution and avoid gritty texture, which is generally present in direct compressible sugar. The tablets obtained are strong and can be packed in conventional packing in to bottles and blisters.

Wow tab technology:

Yamanouchi patented this technology. WOW means without water. This technology utilizes conventional granulation and tableting methods to produce MDTs employing low- and high-moldability saccharides. Low moldability saccharides are lactose, mannitol, glucose, sucrose, and xylitol. High-moldability saccharides are maltose, maltitol, sorbitol, and oligosaccharides. When these low- and high-moldable saccharides are used alone tablets obtained do not have desired properties of rapid disintegration and hardness, so combinations are used. This technology involves granulation of low-moldable saccharides with high-moldable saccharides as a binder and compressing into tablets followed by moisture treatment. Thus tablets obtained showed adequate hardness and rapid disintegration.

Dispersible tablet technology:

Lek, Yugoslavia patents this technology. It offers development of MDTs with improved dissolution rate by incorporating 8-10% of organic acids and disintegrating agents. Disintegrating agent facilitates rapid swelling and good wetting capabilities to the tablets that results in quick disintegration. Disintegrants include starch, modified starches, microcrystalline cellulose, alginic acid, cross-linked sodium carboxy methyl cellulose and cyclodextrins. Combination of disintegrants improves disintegration of tablets usually less than 1 min.

Pharmaburst technology:

SPI Pharma, New Castle, patents this technology. It utilizes the co-processed excipients to develop MDTs, which dissolves within 30-40 s. This technology involves dry blending of drug, flavour, and lubricant followed by compression into tablets. Tablets obtained have sufficient strength so they can be packed in blister packs and bottles.

Frosta technology:

This technology patents by Akina. It utilizes the concept of formulating plastic granules and compressing at low pressure to produce strong tablets with high porosity. Plastic granules composed of:

- Porous and plastic material,
- Water penetration enhancer, and
- Binder

The process involves usually mixing the porous plastic material with water penetration enhancer and followed by granulating with binder. The tablets obtained have excellent hardness and rapid disintegration time ranging from 15 to 30 s depending on size of tablet.

Oraquick:

This technology is patented by K.V.S. Pharmaceuticals. It utilizes taste masking microsphere technology called as micromask, which provides superior mouth feel, significant mechanical strength, and quick disintegration/dissolution of product. This process involves preparation of microparticles in the form of matrix that protects drug, which can be compressed with sufficient mechanical strength. Low heat of production in this process makes it appropriate for heat sensitive drugs. Oraquick product dissolves within few seconds (M. Swamivelmanickam *et al*., 2010).

CHAPTER-III

LITERATURE REVIEW

Syusuke Sano *et al.,* 2011. Prepared and evaluated of swelling induced –orally disintegrating tablets by microwave irradiation. In this study, to improve the opposing properties in a molded tablet using a one - step procedure that exploits the swelling induce by microwave treatment. Swelling of microwave irradiation observed high ratio of silicon dioxide and low levels of water volume. The results indicate that the disintegration time was clearly shortened by indication of the swelling. It was concluded that the one-step method using microwave irradiation would be useful method for preparing the ODTs.

Sona P.S. *et al.,* 2011. Formulated and evaluated taste masked orally disintegrating tablets of Diclofenac sodium. In this study, the bitter taste of Diclofenac sodium was masked by adding Veegum (Magnesium aluminium silicate). Granules of Diclofenac sodium were prepared using different ratio of veegum by wet granulation method. Diclofenac sodium orally disintegrating tablets were prepared by direct compression method using different concentration of two various superdisintegrants like Sodium starch glycolate, Croscarmellose sodium. The formulation containing Croscarmellose sodium has more wetting time than Sodium starch glycolate. It was concluded that the concentration of superdisintegrants increases disintegration time, dispersion time and In-vitro dissolution time decreases. Based on these tests the formulation containing 5% of sodium starch glycolate and croscarmellose sodium were selected as the optimum formulations.

Devakar Rao Kalakuntla *et al.,* 2011. Designed and developed taste masking Lornoxicam orodispersible tablet. The bitter taste of L Lornoxicam was masked by complexation with Eudragit E-100.The drug-Eutragit E-100 polymer complex was prepared by simple mass extrusion technique using syringe. Direct compression method was used to prepare ODT tablets. Two different disintegrants (Indion-414, SSG) in different ratio were used. The results concluded that the formulation containing Indion-414 (6%) was selected as the best formulation .It showed least disintegration time and the high percentage drug release.

Ajaykumar Patil *et al.,* 2011. Formulated and evaluated of mouth dissolving tablets of Montelukast sodium. In this study, the MDT was prepared by direct compression method. Two different superdisintegrants like Croscarmellose sodium, Crospovidone in different concentration were added. The disintegration of the tablets decreased with increase in the concentration of Crospovidone. The rapid drug dissolution was observed in the formulation containing Croscarmellose sodium, this may be attributed to rapid swelling and disintegration of a tablet and so the formulation containing Croscarmellose sodium was selected as the best formulation.

Panwar. A.S. *et al..,* 2011. Formulated and evaluated fast dissolving tablet of Piroxicam. In this study, the FDT was prepared by direct compression method. Using solid dispersion of superdisintegrant like SSG, which improve the disintegration process. The tablet formulation was developed from Piroxicam-SSG (1:4) solid dispersion using microcrystalline cellulose as diluents. Other excipients like aerosol, sodium saccharin were added. It was concluded that the solid dispersion of Piroxicam-SSG markedly improved the dissolution of Piroxicam

powder. Since the formulation SSG included in solid dispersion from was found in much higher concentration than general concentration of solid dispersion in other tablet dosage form.

Kirankumar.B *et al.,* 2011, formulated developed and evaluated fast dissolving tablet of carvedilol using superdisintegrants and solid dispersion technique. In this study, the fast dissolving tablets were prepared using superdisintegrants like Ac-Di-Sol, SSG and polymer is PEG by solid dispersion with dry granulation method. The formulation containing Drug-PEG 4000 (1:4) by using combination of two superdisintegrants in 2 % concentration showed the best drug release. This ensures that solid dispersion technique have reduced the drug particle size and changes the microenvironment of the drug particles, which increases the rate of dissolution and absorption of poorly water soluble drugs.

Sunil Makwana.H *et al.,* 2010, Formulated and evaluated taste masked Orodispersible tablet of Ondansetron hydrochloride .The bitterness taste of Ondansetron hydrochloride was masked by making drug-resin complex with Indion-204.The drug-resin complex was prepared by batch method. Drug-resin complex were optimized by considering parameters such as resin concentration, swelling time, stirring time, pH, temperature on maximum drug loading. The Ondansetron hydrochloride Orodispersible tablet was prepared by direct compression method. Indion-414 was selected as a superdisintegrant. The dissolution studies of tablets showed more than 90% of drug release within 15 minutes. The complexation of Ondansetron HCL with Indion-204 increases acceptability and palatability of formulated rapid disintegrating tablets within 15 minutes.

Dipti Gohil.Y. *et al.,* 2010, Formulated and characterised Bambuterol hydrochloride fast dissolving tablet using various superdisintegrants. In this study, the FDT formulations were prepared by direct compression method by using different concentrations of various superdisintegrants such as SSG, CP, CCS and Pregelatinised starch. In dissolution studies, the maximum increase in the dissolution rate was observed with 12 % crospovidone amongst the superdisintegrants. The order of enhancement of the dissolution rate with various superdisintegrants was found to be Crospovidone > Croscarmellose sodium > Sodium starch glycolate > Pregelatinised starch.

Venkada Ramana Reddy.S *et al.,* 2010, Formulated, developed and compared different compressed oral disintegrating tablets. The ODT formulations were prepared by using different drug like Granisetron hydrochloride, Memantine hydrochloride, Amlodipine besylate and Zaleplon ODT formulation were prepared by direct compression method. Desloratadine, Risperidone ODT formulations were prepared by wet granulation technique by using taste masking ion exchange resin because of its bitterness taste. Amberlite was used as a taste masking agent and croscarmellose sodium was used as a superdisintegrant.It was concluded that all the formulation with improved taste masking and quick disintegration time and drug release achieved within the short time.

Puttewar. T.Y *et al.,* 2010, Formulated and evaluated orodispersible tablet of taste masked doxylamine succinate using ion exchange resin .To prevent bitter taste and unacceptable odour of the drug, the drug was taste masked with weak cation exchange resins like Indion-234, Indion-204 and Indion-414. Drug-resin complex was prepared by using batch method and effect of various processing parameters viz

drug-resin ratio, pH, temperature and drug concentration was optimized the loading conditions. A taste masking of resinate was confirmed by time intensity method and drug release characteristics. Doxylamine succinate Orodispersible tablets were prepared by direct compression method by using Crospovidone as a superdisintegrant.It was concluded that Crospovidone containing formulation exhibit lowest disintegration time and highest drug release and so this formulation was considered as a best formulation.

Dahima Rashmi *et al.,* 2010, Formulated and evaluated taste masked Orodispersible tablet of Metaclopramide hydrochloride using Indion-204.The drug resinate complex was prepared by using Indion-204 which is used to mask the bitter taste of Metaclopramide HCL. The DRC was prepared by batch process. The cation ion exchange resin Indion-204 was selected. The various parameters such as resin concentration, swelling time, stirring time, pH and temperature were optimized on maximum drug loading. The Orodispersible tablet of metaclopramide tablet was prepared by direct compression method. The dissolution studies of the tablets reveals that more than 85% of the drug was released within ten minutes. The complexation of Metaclopramide hydrochloride with Indion-204 increases the acceptability and palatability of formulated rapid disintegrating tablets.

Antaryami Jena *et al.,* 2010, Formulated and evaluated taste masked orally disintegrating Ondansetron hydrochloride tablet. In this study, the bitter taste of Ondansetron hydrochloride was masked by complexation with ion exchange resin indion-294.The DRC was prepared by wet granulation method. The drug-resin concentration was selected by maximum drug loading on resin. The ODT formulation of Ondansetron was prepared by wet granulation method using different

types of superdisintegrants like Croscarmellose sodium, Crospovidone and Indion-234. Formulation containing Indion-234(5%) was selected as the best formulation. It showed less disintegration time and more drug release.

Sukas Kakade.M *et al.,* 2010, Formulated and evaluated mouth dissolving tablets of Losartan potassium by direct compression technique.In this studies, the MDT formulation were prepared by direct compression technique using different concentration of various superdisintegrants like Polyplasdone XL-10, Croscarmellose sodium and Explotab.The results showed that among three superdisintegrants ,Polyplasdone XL-10 showed less disintegration time than others. The reason may be high gelling tendency of Croscarmellose sodium and Explotab than Polyplasdone XL-10, which causes swelling tablet mass with subsequent retardation of disintegration. It was concluded that the relative efficiency of these superdisintegrants to improve the disintegration and dissolution rate of tablets was in the order Polyplasdone XL-10 > Croscarmellose sodium > Explotab.

Inderbir Singh *et al.,* 2010, Masked the unpleasant taste of Etoricoxib by crosslinked acrylic polymer based ion exchange resin complexation. In this study, the bitter taste of Etoricoxib was masked by complexation with weak cation exchange resin indion-234. Drug-resin complex was prepared by batch method. 1:2 drug-resin complexes was found to be better taste masking properties .Drug-resin complex were evaluated by sensory taste evaluation test, FTIR and XRD analysis methods. The taste masked Etoricoxib tablets were prepared by direct compression method. The effective tablet disintegration was due to extensive swelling properties of the selected resins. It was concluded that complexation of Etoricoxib with cation exchange resin was found to increase the acceptability and palatability of the drug.

Raghaveendra. N.G. *et al.,* 2010, Developed of fast dissolving carbamazepine tablets; effect of functionality of superdisintegrants. Carbamazepine FDT's were prepared by direct compression method using different superdisintegrants such as CCS, CP and SSG in various concentrations. Disintegration and dissolution parameters decreased with increase in the level of CCS and CP, where as disintegrating and dissolution parameters increased with increase in the level of SSG in tablets. It was concluded that the formulation containing CCS (105) was best formulation it showed enhanced dissolution will leads to improved bioavailability, effectiveness and better patient compliance.

Shankar Aulapati *et al.,* 2010, Formulated and evaluated taste masked disintegrating Losartan potassium tablets. In this study, Losartan potassium fast disintegrating tablets were prepared by direct compression method using different concentration of various superdisintegrants like Crospovidone, Croscarmellose sodium and Sodium starch glycolate were added. The dissolution profiles showed that the higher concentration of crospovidone results in rapid disintegration of tablets in dissolution medium resulting in optimized drug release from tablet formulation.

Metker Vishal *et al.,* 2010, Formulated and evaluated orodispersible tablets of Lornoxicam. The orodispersible tablet of lornoxicam were prepared by wet granulation technique using Kyron T-314 as superdisintegrator and menthol as subliming agent .It was concluded that the sublimation method showed better disintegration and drug release. The rapid dissolution was due to easy breakdown of particles due to porous structure formation after sublimation of menthol and rapid absorption of drugs into the dissolution medium. The formulated orodispersible

tablets disintegrate within few seconds without need of water, thereby enhancing the absorption leading to its increased bioavailability.

Ganesh Kumar Gudas *et al.,* 2010, Formulated and evaluated fast dissolving tablets of Chlorpromazine hydrochloride. The FDT formulations were prepared by direct compression method. Various concentrations of five different superdisintegrants such as SSG, CP, CCS, L-HPC and Pregelatinised starch were added. Excipients like MCC, Mannitol, Aerosol, Aspartame, Magnesium stearate, Strawberry flavour were added to the formulation. The results showed that the order of enhancement of the dissolution rate with various superdisintegrants was found to be CP> CCS > SSG > L-HPC >Pregelatinised starch. Co-grinding of all the excipients before compression resulting the increase in the solubility. It was concluded that chlorpromazine-HCL FDT was successfully prepared with selected superdisintegrants in order to improve disintegrant / dissolution of drug leads to better patient compliance and effective therapy.

Jeevana Jyothi .B *et al.,* 2010, Developed fast dissolving tablets of Glibenclamide using Crospovidone and its kneading mixture. The fast dissolving tablets were prepared by wet granulation method. The kneading mixture of glibenclamide was prepared with Crospovidone in various concentrations. Glibenclamide-Crospovidone (1:1.5) formulation was showed maximum amount of drug release. So it was selected as best formulation.

Ashwini Madgulkar.R *et al.,* 2009, Formulated designed and optimized novel taste masked mouth dissolving tablets of tramadol having adequate mechanical strength. This MDT formulation was prepared by direct compression technique. The bitterness taste of tramadol HCL was masked by making drug-resin complex with

Tulsion 335.A 3^2 full factorial design and statistical models were applied to optimized the effect of superdisintegrant and mouth dissolving binder. It was concluded that the bitter taste of tramadol can be masked by forming ion exchange complex with tulsion335.The MDT formulation of tramadol having rapid disintegration and good mechanical strength achived by adding a novel combination of crospovidone and gelucire 39/01.

Rajnibala *et al.,* 2009, Developed – bitter zolpidem tartrate mouth dissolving tablet. The bitterness of zolpidem tartrate was masked by preparation of Drug-Resin comlex and Drug-Resin granules.Tulsion335 was used as a taste masking agent. The MDT of both resinates and granules were prepared with two different superdisintegrants. The MDT formulation was prepared by superdisintegrant addition method .Croscarmellose sodium and Crospovidone were added to the formulation as a superdisintegrant in various concentrations. It was concluded that the tablet containing Crospovidone has less disintegration time, fast and more drug release.

Mahajan.K.G. *et al.,* 2009, Formulated characterised and evaluated rapid disintegrating tablet of Atifloxacin sesquihydrate by ion exchange resin technique. In this study, the bitterness taste of Atifloxacin sesquihydrate was masked by Indion-204, Indion-214, Indion-234, Tulsion-335 ion exchange resins. The selection of drug-resin complex ratio was observed by maximum percentage of a drug loading on resin. The MDT formulation was formulated by wet granulation method using different concentration of Sodium starch glycolate, Croscarmellose sodium and Crospovidone as the superdisintegrants. Formulation containing

Crospovidone (8%) was selected as the best formulation. It showed less disintegration time, good hardness, short wetting time and high drug release.

Raval S.B *et al.,* 2009, Formulated and evaluated tramadol hydrochloride Mouth dissolving tablet. The bitter taste of Tramadol hydrochloride was masked by using indion-294 ion exchange resin. The taste masked granules of drug and resin were prepared by wet granulation method. Drug-resin ratio 1:2 showed better results than other drug-resin ratio .The mouth dissolving tablet of Tramadol hydrochloride was prepared by using direct compression method using different concentration of superdisintegrants like Croscarmellose sodium, Crospovidone and Indion-234. It was concluded that the MDT formulation containing Indion-234 (6%) as a superdisintegrant was the best formulation which showed the maximum percentage of drug release.

Brahmenshwar Mishra *et al.,* 2009, Fabricated and evaluated taste masked resinate of Risperidone and its orally disintegrating tablets. The bitter taste of Risperidone was masked by making Drug-Resin complex with Amberlite IRP 64.The taste masked drug resinate was formulated by batch method. The various parameters were optimized like drug-resin ratio, pH medium, temperature and exposure time on maximum drug loading. The Risperidone Orally disintegrating tablet was prepared by direct compression method using Crospovidone as a superdisintegrant. 92% of drug release was released from the complex contained ODT within 5 minutes.

Biraju Patel *et al.,* 2009, developed and evaluated of fast dissolving tablets of glipizide.In this study, the glipizide FDTs were prepared by direct compression method. Two different superdisintegrants like Croscarmellose sodium,

Crospovidone were added in different concentration. Formulation containing Croscarmellose sodium (5%) with PVP K30 was selected as the optimized formulation. This formulation was compared with marketed conventional formulation .It was concluded that the superdisintegrant based fast dissolving tablets of glipizide would providing quick onset of action without need of water for swallowing or administration.

Rikki Laitinen *et al.,* 2009, Intra orally fast dissolving particles of a poorly soluble drug; preparation and invitro characterization. In this study, the dissolution rate of poorly soluble drug; perphanazine was improved by a solid dispersion technique.PVP K30 and PEG-8000 were selected as a carriers. Freeze drying method was used to preparation of solid dispersion technique. The dissolution rate of perphenazine was improved with all the drug polymer mixture ratio was compared to crystalline or micronized perphenazine.A major dissolution rate improvement was seen with perphenazine: PEG (1:5) formulation. It was concluded that the formulation of HCL salt and solid solutions promoted the dissolution of perphenazine.

Raguia Ali Shoukri *et al.,* 2009, Studied *In-vitro* and *In-vivo* evaluation of Nimesulide in lyophilized orally disintegrating tablets. Nimesulide, a drug with poor solubility and poor bioavailability was enhanced by formulating orally disintegrating tablet. The nimesulide orally disintegrating formulation was prepared by freeze drying technique. In this technique, aqueous dispersion of nimesulide, A sugar alcohol and a collapsed protectant with different disintegration accelerators were added .Results obtained from dissolution and disintegration studies showed that lyophilized ODT's disintegrate within few seconds and showed significantly

faster dissolution rate nimesulide compared to the plain powder drug and commercially available immediate release nimesulide tablets.

Jain C.P *et al.,* 2009. Formulated and evaluated domperidone fast dissolving tablets .In this studies, the domperidone FDT's were prepared by direct compression method using SSG as superdisintegrant such as CP,CCS and SSG. SSG swells with more gelling than CCS and CP, which extent disintegration time. As the concentration of superdisintegrants in the formulation increased in the disintegration time was found to decrease.SSG is disintegrates in swelling mechanism leading to longer wetting time. CP and CCS perform their disintegrating action by wicking through capillary action and fibrous structure, respectively with minimum gelling. In the release studies showed concentration of superdisintegrant increased the drug release also increased. The release rate was found to follow order; CP>CCS>SSG.

Parmar.R.B. *et al.,* 2009, Formulated and evaluated Domperidone fast dissolving tablets. In this study, the domperidone FDT was prepared by direct compression method using SSG as the superdisintegrant. Other excipients such as avicel PH 102, mannitol, lactose, talc and magnesium stearate were added and compressed into tablets. The best formulation was selected depends upon the disintegrating efficiency and rapid dissolution. The best formulation was further compared to the marketed preparation. It was concluded that the dissolution rate of domperidone was enhanced by a great extent by the addition of superdisintegrant.

Shailendra Kumar Singh *et al.,* 2009, Studied fast disintegrating combination tablets of Omeprazole and domperidone. In this study, the FDT formulation was prepared by direct compression method. Three various superdisintegrants such as kollidon-CL, Ac-Di-Sol and Sodium starch glycolate were added in different

concentration. Tablets prepared with Ac-Di-Sol (4.776%) had less wetting time and minimum water absorption ratio. In dissolution studies, the formulation containing Ac-Di-Sol (4.76%) showed 99% of drug release in 30 minutes. It was concluded that this formulation was best formulation than other formulation.

Pushpendra Kumar. A *et al.,* 2009, Formulated and evaluated fast dissolving tablets of Rupatadine fumarate. In this study, the FDT of Rupatadine fumarate was prepared by direct compression method. Three various superdisintegrants such as Ac-Di-Sol, Polyplasdone and Primojel were added in different concentration .It was concluded that, increase in concentration of superdisintegrants disintegration time decreases in the order of Ac-Di-So < Polyplasdone –XL < Primojel. Dissolution studies of the tablets containing Ac-Di-Sol (5%) showed rapid dissolution as increase the concentration of superdisintegrants.

Ajay Banga. k. *et al.,* 2009, Studied effects of disintegrating promoting agent, lubricants and moisture treatment on optimised fast disintegrating tablets. In this study, the effects of calcium silicate (disintegration promoting agent) and lubricants (magnesium stearate) on an optimized β-cyclodextrin-based fast disintegrating formulation. A 3^2 full factorial design was used to optimize the concentration of calcium silicate and lubricant. It was concluded that 1.5% magnesium stearate concentration was selected as an optimum. It showed optimum hardness value with low disintegration time. Moisture treatment increased hardness of the fast disintegrating tablets. It delayed the tablets disintegration.

Zade. P.S *et al.,* 2009, Formulated evaluated and optimized fast dissolving tablet containing Tizanidine hydrochloride. In this study, the bitter taste of tizanidine hydrochloride was masked by complexation with Eudragit E-100 polymer. This

taste masked granules of drug-Eudragit E-100 were prepared by simple mass extrusion technique with syringe. The FDTs was prepared by direct compression method using different concentration of three superdisintegrants such as SSG, CCS and CP. Other tablets were prepared by sublimation method using camphor as a sublimating agent. The results showed that formulation containing crospovidone (5%) was selected as the optimized formulation .This formulation has the less disintegration time and more drug release. The tablet prepared with camphor (30%) was the best formulation in sublimation method. Comparison of tablets prepared by two methods, it was concluded that superdisintegration method was superior to sublimation method.

Margret Chandira.R *et al.,* 2008, Formulated and evaluated taste masked fast dissolving tablets of Ondansetron-HCL. The bitter taste of Ondansetron-HCL was masked by making drug-resin complex and drug-cationic polymer granules. The drug-resin complex was prepared with Indion-204 and drug-cationic polymer granules were prepared with Eudragit-E100 by time intensity method. The Ondansetron-HCL FDT was formulated by direct compression method using different superdisintegrant such as Indion-414, croscarmellose sodium in different concentrations. DRC formulation containing Indion-414 (2.5%) and the drug-Eudragit E100 granules containing Indion-414 was considered as the best formulation .It showed less disintegration time and more drug release.

Shagupta Khan *et al.,* 2007, Prepared taste masked ondansetron hydrochloride rapid disintegrating tablets by polymer carrier system. In this study, the bitter taste of Ondansetron-HCL was masked by complexation with Eudragit-EPO polymer (amino alkyl methacrylate copolymer) .The Drug-Eudragit EPO was prepared by

precipitation method. Crospovidone was selected as the superdisintegrant added in this formulation .Micro crystalline cellulose and spray-dried mannitol (1:1) as a diluent and various concentration of superdisintegrants were added. The rapid disintegrating tablets were prepared by direct compression method. Polyplasdone XL-10 (7%) was selected as the optimum concentration. This showed minimal disintegration time. It was concluded that the FDT formulation were successively prepared with complete taste masking, rapid disintegration and dissolution was achieved.

CHAPTER-IV

AIM OF WORK

The aim of present work was an attempt to prepare bitterless fast dissolving tablet of desloratadine using weak cation exchange resin indion-234.

Fast dissolving tablets are non-invasive patient friendly drug delivery systems which do not need water and improves pediatric and geriatric compliance. If the drug dissolves and getting absorbed in the mouth it may bypass enterohepatic circulation and prevent first pass metabolism. By this way it may improve the bio availability and dose related side effect of drug. Drugs which are unstable in acidic environment of stomach or alkaline environment of intestine can be administered by this route. Fast dissolving tablet should disintegrate very fast as it is administered in the oral cavity. And so, the drug release and onset of action acheived within short time.

Desloradatine is chemically 8-chloro-6, 11-dihydro-1-(4-piperidinylidine-5H-benzo [5,6] cyclohepta[1,2-b] pyridine, which is an active descarboethoxy metabolite of loratadine. It is a specific, selective peripheral H_1-receptor antagonist relatively non-sedating or second generation anti-histamine. It suppresses release of histamine from human mast cells.

Desloratadine is a white to off-white powder having bitter in taste. To prevent bitter taste, the drug was complexed with cation exchange resin like indion-204 & indion-234(DRC). The fast dissolving tablet was prepared by direct compression method with

superdisintegrant like sodium starch glycolate, crospovidone, croscarmellose sodium and other excipients.

CHAPTER-V

PLAN OF WORK

PART-1

PREFORMULATION STUDIES:

a) Determination of λ-max of desloratadine in pH 5.8 and 0.1 N Hydrochloric acid.

b) Calibration curve for the desloratadine in pH 5.8 and 0.1 N Hydrochloric acid.

PART-2

1) Preparation of drug-resin complex.

2) Selection of ion exchange resin.

PART-3

INTERACTION STUDIES:

1) Differential scanning calorimetric (DSC) studies

2) Fourier Transform Infra Red Spectroscopic (FT-IR) studies

PART-4

Formulation of fast dissolving tablet of desloratadine

PART-5

1) Precompression evaluation of powder blend.

2) Post compression evaluation of prepared tablet.

CHAPTER-VI

MATERIALS AND EQUIPMENTS

MATERIALS	SUPPLIERS
Desloratadine	Enaltec Labs, Chennai, India.
Indion-234	Madras Pharmaceuticals, Chennai, India.
Sodium starch glycolate	Octis Research Lab, Uttarkhand, India.
Crospovidone	Octis Research Lab, Uttarkhand, India.
Croscarmellose sodium	Octis Research Lab, Uttarkhand, India.
Microcrystalline cellulose	High purity laboratory chemicals, Mumbai, India.
Mannitol	Universal Scientific Appliances, Madurai, India.
Saccharin sodium	Universal Scientific Appliances, Madurai, India.
Peppermint flavour	Universal Scientific Appliances, Madurai, India.
Magnesium stearate	Universal Scientific Appliances, Madurai, India.
Talc	Universal Scientific Appliances, Madurai, India.

EQUIPMENTS	SUPPLIERS
Electronic Weighing Balance	A & D Company HR 200, Japan.
Single Punch Tablet Compression Machine	Cadmach, Ahmedabad, India.
UV- Visible Spectrophotometer	Shimadzu, Japan.
Digital Tablet Dissolution Test Apparatus	Disso 2000, Lab India, New Mumbai, India.
Friability Test Apparatus	Indian Equipment Corporation, Mumbai, India.
Hot Air Oven	Rands Instruments, Chennai, India.
Disintegration Test Apparatus	Rolex, India.
Tablets hardness tester (Monsanto)	Pravin Enterprises, Bangalore. India.
Vernier Caliper	Linker, India.
Magnetic stirrer	M.C.Dalal&co, Chennai, India.
Differential Scanning Calorimeter	T.A.Instrument, USA.

CHAPTER-VII

DRUG PROFILE

DESLORATADINE

http://www.drugbank.com., http://www.chemblink.com

Synonyms

- Descarboethoxyloratadine.
- Descarboethoxyloratidine.
- Desloratidine.

Categories

- Second generation antihistamines.
- Cholinergic Antagonists.
- Histamine H1 Antagonists, Non-sedating.

Chemical Name

8-chloro-6,11-dihydro-11-(4-piperidinylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine.

Molecular Formula

$C_{19}H_{19}ClN_2$.

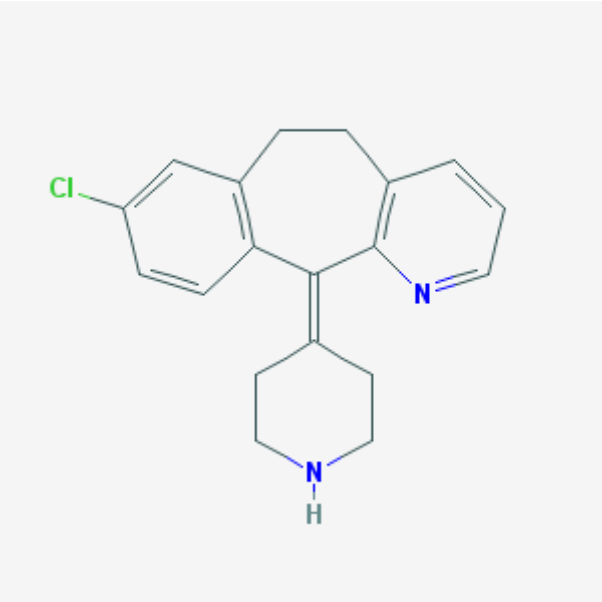
Description

Nature - White to off white powder.

Solubility- Slightly soluble in water but very soluble in ethanol and propylene glycol.

Molecular weight-310.8

Molecular Structure



PHARMACODYNAMIC PROPERTIES

Clinical pharmacology

Mechanism of action

Desloratadine competes with free histamine for binding at H_1-receptor in the GI tract, uterus, large blood vessels and bronchial smooth muscles. This block the action of endogenous histamine, which subsequently leads to temporary relief of the negative symptoms brought on by histamine.

PHARMACOKINETICS

Absorption

- Mean peak plasma concentrations of desloratadine are reached within 3 hours.
- Neither food nor grape fruit juice had an effect on the bioavailability of desloratadine.

Distribution

- Desloratadine is approximately 82-87% bound to plasma protein.
- Protein binding not altered in patients with renal impairment.

Metabolism

- Desloratadine is metabolized to an active metabolite,3-hydroxydesloratadine.This metabolite subsequently undergoes glucuronidation.
- Some individuals (7%) are slow metabolizers of desloratadine and may be more susceptible to dose related adverse events.

Excretion

- Half- life of desloratadine is 27 hours.
- Approximately 87% excreted as metabolic products in urine and feces in equal proportions.
- Desloratadine and 3-hydroxydedloratadine are poorly removed by hemodialysis.

DOSAGE AND ADMINISTRATION

- The dose of desloratadine is 5mg daily.
- In patients with liver or renal dysfunction, a starting dose of 5mg every other day is recommended.

Administration

Administer conventional tablets, oral solution, orally disintegrating tablets and fixed combination extended release tablets.

INDICATIONS AND USES

- Symptomatic relief of nasal and non nasal symptoms of Perennial Allergic Rhinitis.
- Symptomatic treatment of Pruritus and Urticaria (hives) associated with Chronic Idiopathic Urticaria.

Contraindications

- Pharyngitis
- Dry mouth
- Myalgia

- Fatigue
- Somnolence
- Dysmenorrhea
- Diarrhoea
- Fever
- Coughing
- Vomiting
- Upper Respiratory Tract infection

CHAPTER-VIII

CROSPOVIDONE

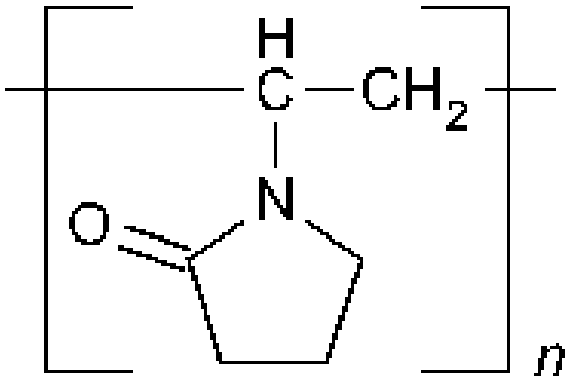
Synonyms:

- Cross linked Povidone.
- Kollidon.
- Polyplasdone.
- Polyvinylpoly pyrrolidone.
- 1-vinyl-2-pyrrolidinone homopolymer.

Chemical Name:

1-Ethenyl-2-pyrrolidinone homopolymer.

Chemical Structure:



Empirical formula:

$(C6H9NO)_n$

Molecular Weight:

>1 000 000

Functional category:

Tablet disintegrant.

Application in Pharmaceutical formulation:

- Tablet disintegrant and dissolution agent.
- Solubility enhancer for poorly soluble drug.

Description:

Crospovidone is a white to creamy-white, finely divided, freeflowing, practically tasteless, odorless or nearly odourless, hygroscopic powder.

Stability and storage condition:

Crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

Incompatibilities:

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adduct with some materials.

Handling Precautions:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended. (Hand book of Pharmaceutical excipients-5th edition, 214-216)

CROSCARMELLOSE SODIUM

Synonyms:

- Ac-Di-Sol.
- Cross linked carboxymethylcellulose sodium.
- Explocel.
- Modified cellulose gum.
- Primellose.
- Solutab.
- Vivasol.

Chemical Name:

Cross linked carboxy methyl ether Cellulose sodium salt.

Functional Category:

Tablet and capsule disintegrant.

Applications in Pharmaceutical Formulation:

Disintegrating agent for tablets and capsules.

Description:

-White or grayish white powder.

-Odourless and tasteless.

-Insoluble in water. Practically insoluble in acetone, ethanol and toluene.

Pharmacopoeial Specifications:

pH (1% w/v dispersion) 5.0–7.0

Loss on drying ≤10%

Heavy metals ≤10 ppm

Sodium chloride and sodium glycolate ≤ 0.5%

Sulfated ash 14.0–28.0%

Settling volume 10.0–30.0 ml

Acidity/alkalinity: pH = 5.0–7.0 in aqueous dispersions.

Density (bulk): 0.529 g/cm3

Density (tapped): 0.819 g/cm3

Density (true): 1.543 g/cm3

Stability and Storage Conditions:

Croscarmellose sodium should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.

Handling Precautions:

Croscarmellose sodium may be irritant to the eyes; eye protection is recommended (Hand book of Pharmaceutical excipients-5th edition, 211-213).

SODIUM STARCH GLYCOLATE

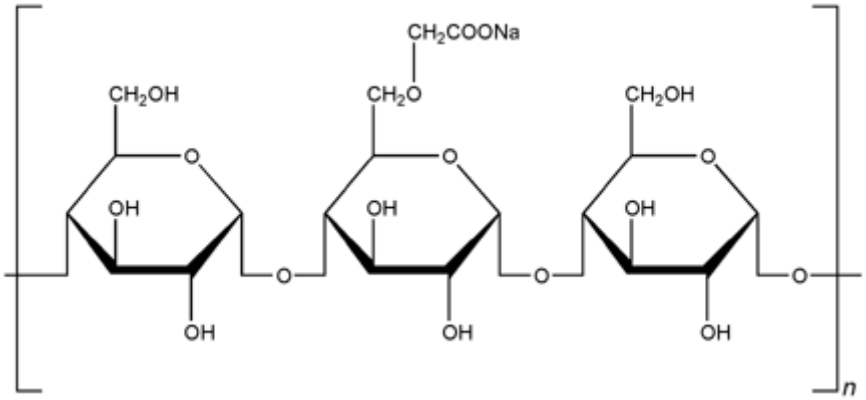
Synonyms:

- Explosol.
- Explotab.
- Primojel.
- Starch carboxymethyl ether, sodium salt.
- Tablo.
- Vivastar P.

Chemical Name:

Sodium carboxymethyl starch.

Chemical structure:



Functional Category:

Tablet and capsule disintegrant.

Application in Pharmaceutical Formulation:

- Sodium starch glycolate is used as a disintegrant in capsule and tablet formulations.
- Sodium starch glycolate is also used as a suspending vehicle.

Description

- Sodium starch glycolate is a white to off-white, odorless, tasteless, free flowing powder
- It does not melt, but chars at approximately 200^{o}C
- It is sparingly soluble in ethanol (95%) but practically insoluble in water.

Pharmacopoeial Specifications:

- Specific surface area: 0.24m2/g;
- Swelling capacity: In water, sodium starch glycolate swells to up to 300 times its volume.
- Viscosity (dynamic): 4200 mPa s (200 cP) for a 4% w/v aqueous dispersion.
- Viscosity is 4.26 mPa s for a 2% w/v aqueous dispersion.

Stability and Storage Conditions:

Sodium starch glycolate should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking.

Incompatibilities:

Sodium starch glycolate is incompatible with ascorbic acid.

Handling Precautions:

Sodium starch glycolate may be irritant to the eyes; eye protection and gloves are recommended. .(Hand book of Pharmaceutical excipients-5th edition)

INDION 234

Description:

INDION 234 is a high purity pharmaceutical grade weak acid cation exchange resin supplied as a dry powder in potassium form. It is suitable for use in pharmaceutical applications for tablet disintegration and taste masking of bitter drugs. INDION 234 is based on cross linked polyacrylic acid.

Applications:

Tablet disintegration

INDION 234 is an effective tablet disintegrant which provides the necessary hardness and chemical stability to the tablet. The product swells up considerably (about 300%) when in contact with water or gastro-intestinal fluids, causing rapid disintegration without the formation of lumps. Depending on the formulation, the use of 0.5% to 5% of INDION 234 is recommended for effective disintegration of the tablet.

Some of the advantages of using INDION 234 as tablet disintegrant are:

- Remarkable swelling tendency on wetting, causing rapid disintegration.
- No lump formation on disintegration.
- Compatible with commonly used therapeutic agents and excipients.
- Works equally efficiently in hydrophilic and hydrophobic formulations.
- Gives good mechanical strength to the tablet,
- Facilitating easy packing and transportation.
- Does not dissolve or have an adhesive tendency as in case of gums.
- Does not stick to punches and dyes.

Characteristics properties:

- Appearance –white to off-white free flowing powder.
- Matrix -crosslinked acrylic polymer.
- Functional Group -carboxylic acid.
- Ionic form as supplied -potassium
- Solubility -Insoluble in water and in common solvents.

Specifications

- Particle size distribution Retained on 100 BSS mesh (150 microns) ; 1.0%,maximum
- Retained on 200 BSS mesh (75 microns) ;70%,minimum
- Moisture content ; 10%,maximum
- Exchangeable potassium ; 5.25 meq/dry g, minimum
- pH of 10% slurry ; 7-9

Taste masking agent

The principle behind the technique of making a formulation tasteless with the help of INDION 234 is very simple and does not involve major capital investment. The complex is made from the drug and INDION 234. The nature of the complex is such that the average cation concentration of about 40 meq/I and pH of 6.7 in saliva is not able to break the complex

The complex is weak enough to be broken down by the hydrochloric acid present in the stomach. Thus the complex is absolutely tasteless and stable, with no after taste, but at the same time its bio-availability is not affected. The above technique has been

found to be helpful in formulation of dosage forms such as dispersible tablets, chewable tablets, chewing gums and oral suspensions.

Toxicity

INDION 234 is a high molecular weight polymer. It is not absorbed by body tissue and is totally safe for human consumption. Tests for toxicological tolerance show that it does not have any pronounced physiological action at recommended dosage and is definitely non- toxic. Experiments on mice have shown LD 50 value for INDION 234 to be approximately 10,000 mg/kg body weight.

Packing

HDPE carbouys with inner double plastic liner bags

Storage

INDION 234 is hygroscopic in nature. It is therefore essential to store it in a tightly packed container to prevent absorption of atmospheric moisture. If moisture is absorbed, the INDION 234 can be dried at 900 C to 1000 C for approximately 6 hours to reduce the moisture content below 10 (Inderbir Singh *et al*., 2007).

MAGNESIUM STEARATE

Synonyms:

- Magnesium octadecanoat.
- Octadecanoic acid, magnesium salt.
- Stearic acid, magnesium salt.

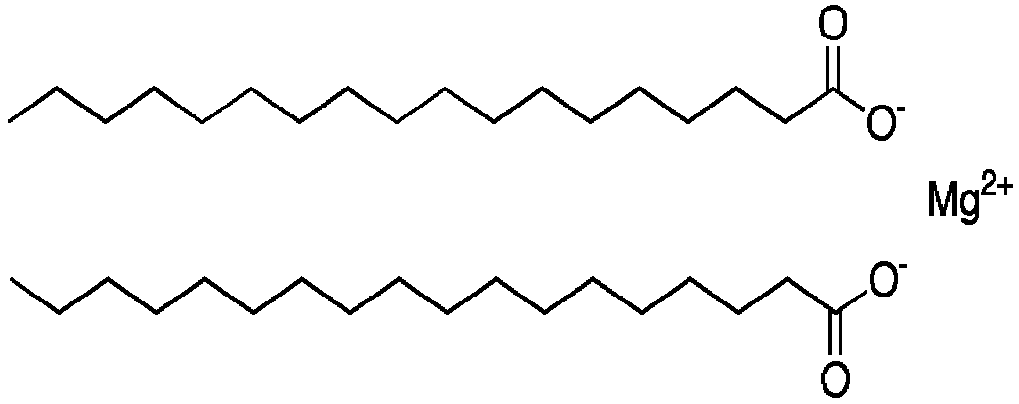
Chemical Name:

Octadecanoic acid magnesium salt.

Structural Formula:

$[CH_3 (CH_2)_{16}COO]_2Mg$

Molecular Structure:



Empirical Formula and Molecular Weight:

$C_{36}H_{70}MgO_4$ & 591.34

Functional Category:

Tablet and capsule lubricant.

Application in Pharmaceutical Formulation:

- Lubricant in capsule and tablet formulation.(0.25% to 0.25%).
- Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations.
- It is also used in barrier creams.

Description:

- Magnesium stearate is a very fine, light white powder.
- Faint odour.
- Characteristic taste.
- Greasy to the touch and readily adheres to the skin.

Pharmacopoeial Specifications:

Freezing point	5538C
Nickel	45 ppm
Cadmium	43 ppm
Loss on drying	46.0%
Chloride	40.1%
Sulfate	41.0%
Lead	410 ppm

Stability and Storage Conditions:

Magnesium stearate should be stored in a well closed container in a cool, dry place.

Incompatibilities:

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

Safety:

Oral consumption of large quantities may produce a laxative effect or mucosal irritation.

Handling Precautions:

- Eye protection and gloves are recommended.

-Excessive inhalation of magnesium stearate dust may cause upper respiratory tract discomfort, coughing, and choking. .(Hand book of Pharmaceutical excipients-5th edition,430-433)

MANNITOL

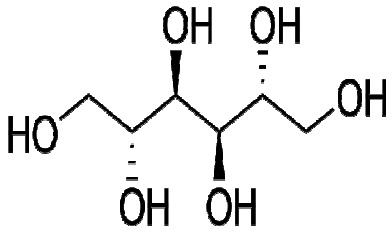
Synonyms:

- Cordycepic acid.
- Manna sugar.
- D-Mannite.
- Pearlitol.

Chemical Name:

D-Mannitol.

Chemical structure:



Empirical Formula and Molecular Weight:

$C_6H_{14}O_6$ & 182.17

Functional Category:

- Diluent.
- Sweetening agent.
- Tonicity agent.

Application in Pharmaceutical Formulation:

- Mannitol is widely used in pharmaceutical formulations and food products.
- It is used as diluents (10–90% w/w) in tablet formulations.

- Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations.
- Plasticizer in soft-gelatin capsules, as a component of sustained-release tablet formulation.
- It is used as a carrier in dry powder inhalers.
- It is also used as diluents in rapidly dispersing oral dosage forms.
- It is used in food applications as a bulking agent.

Description:

- Mannitol is a white, odorless, crystalline powder, or free-flowing granules.
- It has a sweet taste.
- Microscopically, it appears as orthorhombic needles when crystallized from alcohol.
- Mannitol shows polymorphism.

Pharmacopoeial Specifications:

- Density (bulk):0.430 g/cm3.
- Density (tapped):0.734 g/cm3.
- Density (true): 1.514 g/cm3.
- Dissociation constant: pKa = 13.5 at 188C.
- Flowability: powder is cohesive, granules are free flowing.
- Melting point: 166–168^{o}C
- Loss on drying: 40.3%

Stability and Storage Conditions:

It should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

- Mannitol solutions, 20% w/v or stronger, may be salted out by potassium chloride or sodium chloride.
- Mannitol is incompatible with xylitol infusion and may form complexes with some metals such as aluminum, copper, and iron.
- Reducing sugar impurities in mannitol have been implicated in the oxidative degradation of a peptide in a lyophilized formation.

Handling Precautions:

Mannitol may be irritant to the eyes; eye protection is recommended. . (Hand book of Pharmaceutical excipients-5th edition,449-453)

MICROCRYSTALLINE CELLULOSE

Synonyms:

- Avicel PH.
- Celex.
- Celphere.
- Ceolus KG.
- Ethispheres.
- Fibrocel.
- Pharmacel. .
- Vivapur.

Chemical Name:

Cellulose.

Empirical Formula:

$(C_6H_{10}O_5)$ n

Molecular Weight:

36 000

Functional Category:

- Adsorbent.
- Suspending agent, Tablet and capsule diluents, tablet disintegrant.

Application in Pharmaceutical Formulation:

- Microcrystalline cellulose is used as a binder/diluent in oral tablet and capsule formulations.
- Microcrystalline cellulose is used as a lubricant and disintegrant agent in tablet formulation.
- Microcrystalline cellulose is also used in cosmetics and food products.

Description:

Microcrystalline cellulose is a white, odorless, tasteless, crystalline powder composed of porous particles.

Use Concentration (%)

- Adsorbent: 20–90
- Antiadherent: 5–20
- Capsule binder/diluent: 20–90
- Tablet disintegrant : 5–15
- Tablet binder/diluents: 20–90

Pharmacopoeial Specifications:

- pH: 5.0–7.0
- Loss on drying: 47.0%
- Residue on ignition: 40.05%
- Sulfated ash: 40.1%
- Heavy metals: 410 ppm

Typical Properties:

- Density (tapped):0.478 g/cm3,
- Density (true): 1.512–1.668 g/cm3
- Flowability: 1.41 g/s for Emcocel 90M.
- Melting point: chars at 260–2708C.
- Microcrystalline cellulose is hygroscopic.

Stability and Storage Conditions:

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Microcrystalline cellulose is incompatible with strong oxidizing agents.

Handling Precautions:

Microcrystalline cellulose may be irritant to the eyes. Gloves, eye protection, and a dust mask are recommended. .(Hand book of Pharmaceutical excipients-5th edition132-135,)

SACCHARIN SODIUM

Synonyms:

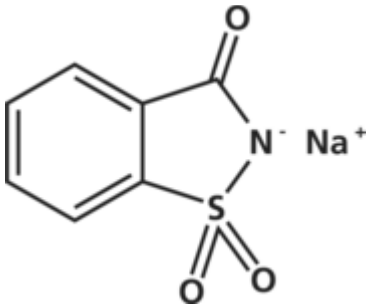
1,2-Benzisothiazolin-3-one 1,1-dioxide, sodium salt; Crystallose E954; sodium o-benzosulfimide; soluble gluside; soluble saccharin; sucaryl sodium.

Chemical Name;

1,2-Benzisothiazol-3(2H)-one 1,1-dioxide, sodium salt for the dihydrate

for the anhydrous material.

Chemical structure:



Empirical Formula and Molecular Weight:

C7H4NNaO3S 205.16

Functional Category:

Sweetening agent.

Application in Pharmaceutical Formulation:

Saccharin sodium is an intense sweetening agent used in beverages, food products, table-top sweeteners and pharmaceutical formulations such as tablets, powders, medicated confectionery, gels, suspensions, liquids, and mouthwashes; It is also used in vitamin preparations.

Uses of saccharin sodium

- Dental paste/gel 0.12–0.3%
- IM/IV injections 0.9%
- Oral solution 0.075–0.6%

Description:

Saccharin sodium occurs as a white, odorless or faintly aromatic, efflorescent, crystalline powder. It has an intensely sweet taste, with a metallic aftertaste that at normal levels of use can be detected by approximately 25% of the population. Saccharin sodium can contain variable amounts of water.

Pharmacopoeial Specification:

- Water 415.0%
- Arsenic 42 ppm
- Selenium 40.003%
- Heavy metals 420 ppm
- Assay (anhydrous basis) 99.0–101.0%

- **Typical Properties**:
- Acidity/alkalinity: pH = 6.6 (10% w/v aqueous solution)
- Density (bulk):0.8–1.1 g/cm3
- Density (particle): 1.70 g/cm3
- Density (tapped): 0.9–1.2 g/cm3
- Moisture content: 14.5% w/w water;
- Solvent Solubility at 208C
- Specific surface area: 0.25m2/g

Stability and Storage Conditions:

Saccharin sodium is stable under the normal range of conditions employed in formulations. Saccharin sodium should be stored in a well-closed container in a cool, dry place.

Handling Precautions:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and a dust mask are recommended. .(Hand book of Pharmaceutican excipients-5th edition)

TALC

Synonyms:

Altalc, E553b, hydrous magnesium calcium silicate, hydrous magnesium silicate, Luzenac Pharma, magnesium hydrogen metasilicate, Magsil Osmanthus, Magsil Star, powdered talc, purified French chalk, Purtalc, soapstone, steatite, Superiore.

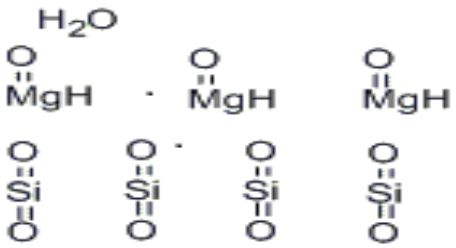
Chemical Name:

Talc

Empirical Formula:

$Mg_6(Si_2O_5)_4(OH)_4$.

Chemical Structure:



Functional Category:

Anticaking agent, glidant, tablet and capsule diluent, tablet and capsule lubricant.

Applications in Pharmaceutical Formulations:

- Lubricant and diluents.
- Dissolution retardant in the development of controlled-release products.
- An adsorbant.
- Dusting powder.

- Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

Dusting powder: 90.0–99.0%

Glidant and tablet lubricant: 1.0–10.0%

Tablet and capsule diluents: 5.0–30.0%

Description:

Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Pharmacopoeial Specifications:

- Acidity/alkalinity: pH = 7–10 for a 20% w/v aqueous dispersion.
- Hardness (Mohs): 1.0–1.5
- Solubility: practically insoluble in dilute acids and alkalis, organic solvents, and water.
- Specific gravity: 2.7–2.8
- Specific surface area: 2.41–2.42m2/g

Stability and Storage Conditions:

Talc is a stable material and may be sterilized by heating at 1608C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation.Talc should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Incompatible with quaternary ammonium compounds.

Handling Precautions:

Talc is irritant if inhaled and prolonged excessive exposure may cause pneumoconiosis. In the UK, the occupational exposure limit for talc is 1 mg/m3 of

respirable dust long-term (8-hour TWA).Eye protection, gloves, and a respirator are recommended (Handbook of Pharmaceutical excipients- 5th edition, 641-643).

CHAPTER-IX

EXPERIMENTAL DETAILS

I. CALIBRATION OF DESLORATADINE IN pH5.8

a) Preparation of pH 5.8 Buffer Solution:

Add 50ml of 0.2M potassium dihydrogenortho phosphate in a 200ml of volumetric flask. Add 3.6ml of 0.2M Sodium hydroxide is added and made upto the volume with distilled water.

b) Calibration curve of Desloratadine in pH 5.8:

An accurately weighed quantity (100mg) of pure Desloratadine is dissolved in sufficient amount of methanol and made upto 100ml with methanol to produce 1mg/ml solution. From this 10ml of the solution is pipetted-out and made upto 100ml with the pH 5.8 buffer solution.From this 2-20ml are pipetted-out and diluted to 100ml with the pH 5.8 buffer solution. The solution is scanned within the range of 200-400 nm in UV-Spectrophotometer.Theabsorbance of the solutions is measured at the λ_{max}.The calibration graph is drawn by taking concentration in X-axis and respective absorbance in Y-axis to get a straight line as per Beers law.

II. CALIBRATION OF DESLORATADINE IN 0.1N HYDROCHLORIC ACID

a) Preparation of 0.1N Hydrochloric Acid Buffer Solution:

Dilute 8.5ml of hydrochloric acid in distilled waterand the volume is made up to 1000 ml.

b) Calibration Curve of Desloratadine in 0.1N Hydrochloric Acid:

An accurately weighed quantity (100mg) of pure Desloratadine is dissolved in sufficientamount of methanol and made upto 100ml with methanol to produce 1mg/ml solution. From this 10ml of the solution is pipetted-out and made upto 100ml with the 0.1N Hydrochloric acid buffer solution. From this 2-20ml arepipetted-out and diluted to 100ml with the 0.1N Hydrochloric acid buffer solution.The solution is scanned within the range of 200-400 nm in UV-Spectrophotometer. The absorbances of the solutions are measured at the λ_{max}.The calibration graph is drawn by taking concentration in X-axis and respective absorbance in Y-axis to get a straight line as per Beers law.

III. PREPARATION OF DRUG-RESIN COMPLEX(DRC)

The drug and resin are passed through a #40 mesh screen prior to mixing.The drug desloratadine is dispersed in purified water (100ml) under stirring by using magnetic stirrer at 100rpm in room temperature (25-27˚C).The pH of the drug dispersion is adjusted to pH 6.5 ±0.5 with 2% W/V citric acid solution. The resin is thenadded to the pHadjusted drug dispersion and stirred for 3 hours.The drug resinate dispersion is filtered through whatmann filter paper No;41 and dried at 60˚C.The dried mass is passed through #24 mesh.(Venkata Ramana Retty.S *et al*., 2010)

IV. SELECTION OF ION-EXCHANGE RESIN(IER)

The DRC is prepared with two different resins viz INDION-204 and INDION-234.In each case, 100mg of Desloratadine in deionised water is stirred with resin containing various drug-resin ratios(1:1, 1:2, 1:3, 1:4, 1:5) by using magnetic stirrerand stirred for 3 hours at 100 rpm in room temperature.Then the dispersion is filtered through Whatmann filter paper No; 41.The amount of drug loaded is determined

indirectly by estimating the amount remaining to be loaded in solution spectrophotometrically at 242 nm in UV-Spectrophotometer. Theresin to which the drug bound to the maximum percentageis selected for further studies. The following formula is used to calculate the percentage of drug bound to resin.

$$\%\text{Drug Bound to Resin} = \frac{(\text{Total amount of drug}) - (\text{unbound drug})}{(\text{Total amount of drug})} \times 100.$$

V. EVALUATION OF DRUG RESIN COMPLEX

a) Fourier Transform-Infra Red (FT-IR)Studies:

Desloratadine,indion-234 and DRC are subjected to Fourier Transform Infra Red Spectroscopy studies (Shimadzu,Japan).Samples are prepared using KBr disc method and spectra are recorded over the range 400-4000 per cm.Spectra are analyzed for drug-resin interaction and functional groups involved in the complexation process.

b) Differential Scanning Colorimetric(DSC) studies:

A Differential Scanning Calorimeter (DSC Q200 V24.4 Build 116) is used. The equipment is calibrated using indium and zinc. Samples are heated at 10°C per minute in aluminium pans under Nitrogen atmosphere. The onset of the melting points and enthalpies of fusion are calculated. The cell had a nitrogen purge flowing approximately at 30 cube cm per minute. The cell and sample are held isothermally at 79°C for 30 minutes to purge the headspace and sample with nitrogen before heating. The cell and sample are then heated to 400°C while monitoring heat flow.

VI. FORMULATION OF FAST DISSOLVING TABLET OF DESLORATADINE

An accurately weighed quantity of drug-resin complex is mixed with different ratio of (1.5%, 3%, 4.5%, 6%, 7.5%) superdisintegrant (Sodium starch glycolate, Crospovidone, Croscarmellose Sodium). The drug-resin complex along with superdisintegrant is mixed with Microcrystalline cellulose, Mannitol, Saccharin sodium and Peppermint flavour in geometrical dilution. Then Magnesium stearate and Talc are added, mixed and compressed into tablets using single punch tablet punching machine to produce flat faced tablets weighing 200mg each with 8mm diameter. The compositions of the different formulation are given in Table-5. (Sona P.S. *et al*., 2011)

VII. PRECOMPRESSION EVALUATION FOR POWDER BLEND

i. Angle of Repose:

The flow characteristics are measured by angle of repose. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

$$\tan \theta = h/r$$

$$\theta = \tan^{-1}(h/r)$$

Where,

h=Height of the pile.

r=Radius of the base of the pile.

θ=Angle of repose.

The angle of repose is determined by fixed funnel method. The powder mass is allowed to flow through the funnel kept on a stand at a fixed height. The powders are carefully poured through the funnel on the piece of paper placed on the horizontal

surface until the apex of conical pile just reached the tip of the funnel. The height of the pile and radius of the conical pile is noted and the angle of repose is calculated by the above said formula. (Priyanka Nagar *et al*., 2011)

ii. Bulk Density:

Bulk density is defined as the mass of the powder divided by the bulk volume;it is expressed as gm/cm^3. A powder blend (10g) is carefully introduced into a 100ml graduated cylinder .The cylinder is dropped onto a hard wood surface three times from a height of 1 inch at two second interval. The bulk density obtained by dividing the weight of samples in gm by final volume in cm^3 (Mukesh.P.Ratnaparkhi *et al*., 2008).

$$\text{Bulk density} = \frac{\text{Mass of powder}}{\text{Bulk volume}} = \frac{m}{V_b}$$

iii. *Tapped Density:*

Tapped density is determined by placing a graduated cylinder, containing a known mass of a drug-resinate excipients blend. The cylinder is allowed to fall under its own weight onto a hard surface from the height of 10cm at 2 second intervals.The tapping is continued until no further change in volume is noted.(Rajashree Panigrahi *et al*., 2010).

The tapped density (Dt) is calculated in g/ml by the formula

$$D_t = m/V_t$$

Where,

m=Weight of the sample powder taken.

Vt=Tapped volume.

iv. Carr's Compressibility Index:

The simplex way of measurement of the free flow of powder is compressibility.(Suhas.M.Kakade *et al*., 2010) Which is calculated by the following formula,

$$\text{Compressibility Index} = \frac{\text{Tapped density-Bulk density}}{\text{Tapped density}} \times 100$$

v. Hausner's Ratio:

Hausner's ratio is an indirect index of ease of powder flow**.** If the Hausner's ratio of the powder is near to 1.25 indicates better powder flow.(Kuldeep V *et al*., 2010). It is calculated by the following formula,

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

< 1.25-good flow.

1.25-poor flow.

vi. *Drug Content:*

5mg equivalent of DRC is stirred with 100ml of 0.1N Hydrochloric acid for 60 minutes so as to release the entire drug from DRC. The mixture is filtered and diluted to 100ml using 0.1N Hydrochloric acid. The absorbance of the solution is measured at 242nm using 0.1 N Hydrochloric acid as blank and the content of desloratadine is estimated (Dahima Rashmi *et al*., 2010).

VIII. POST COMPRESSION EVALUATION

i. Thickness and Diameter:

Tablet thickness and diameter is an important characteristic of the tablets.In reproducing appearance and also in counting by using filling equipment. The thickness and diameter of the fast dissolving tablets are determined by using vernier calliper (Magesh Kumar.K *et al*., 2009).

ii. Hardness:

The hardness of the tablet is indicative of its tensile strength and is measured in terms of load/pressure required to crush it when placed on its edge.The hardness is a function of physical properties of granules like their hardness and deformation under load, binders and above all the compression force. The hardness has influence on disintegration and dissolution times and is as such a factor that may affect bioavailability. The hardness of the tablet is determined by using Monsanto hardness tester. (Puttewar T.Y *et al*., 2010)

iii. Weight Variation Test:

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. First the total weight of 20 tablets from each formulation is determined and the average is calculated. The individual weight of the each tablet is also determined to find out the weight variation. The tablets meets the USP test , If no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limits.(Priyanka Nagar *et al.,* 2011)

USP specification for the uniformity of weight

S.No.	Average weight(mg)	Maximum % difference allowed
1	130 or less	10%
2	130-324 mg	7.5%
3	More than 324 mg	5%

iv. Friability:

Friability is determined using Roche friabilator.10 tablets from each formulation are accurately weighed and placed in the drum of friabilator.The tablets are rotated at 25 rpm for a period of 4 min and then removed,dedusted and accurately reweighed. The percentage loss in weight is calculated and taken as a measure of friability. The weight loss should not be more than 1 **%.**(Raguia Ali Shoukri *et al*., 2009)

$$\text{Percentage friability} = \frac{\text{Initial weight-Final weight}}{\text{Initial weight}} \times 100$$

v. Uniformity of Content:

Ten tablets are selected randomly and powdered them. The average weight is calculated .The average weight of the tablet powder is dissolved in 100ml of 0.1N Hydrochloric acid,stirred for 60 minutes by using magnetic stirrer at 100rpm maintained at room temperature. The dispersion is filtered and collect the filtrate .One ml of filtrate is diluted to 100ml with 0.1N Hydro chloric acid. The absorbance of this solution is measured at 242 nm using 0.1N Hydro chloric acid as blank and content of desloratadine is estimated (Ashwini R.Madgulkar *et al*., 2009).

vi. Wetting Time:

Ten millilitres of distilled water containing Methylene blue,water soluble dye is placed in a petridish of 10cm diameter.Tablets are carefully placed in the centre of the petridish and the time required for water to reach the upper surface of the tablet is noted as the wetting time. Three tablets are selected and the average wetting time is calculated.(Raguia Ali Shoukri *et al*., 2009)

vii. Water Absorption Ratio:

A piece of tissue paper folded twice is kept in a petridish containing 6ml of purified water .The tablet is placed on the tissue paper and allowed to wet completely. The wetted tablet is removed and reweighed(Sukash M.Kakade *et al*., 2010).Water absorption ratio (R) is determined according to the following equation

$$R = \frac{W_a - W_b}{W_b} \times 100$$

Where,

W_b-Weight of the tablet before water absorption.

W_a-Weight of the tablet after water absorption.

viii. In-Vitro Disintegration Time:

The disintegration time is defined as the time necessary for the Fast disintegrating tablet to completely disintegrate until no solid residue remains or only a trace amount of soft residue remains on the screen. Disintegration time is measured in 900 ml artificial saliva (pH 5.8), according to the USP 24 method without disc at 37 $\pm$0.5℃ . The disintegration time of 3 individual tablets are recorded and the average

is reported.As per the European Pharmacopoeia (EP), the orodispersible tablets should disintegrate within 3 minutes (C.P.Jain *et al*., 2009).

ix. In-Vitro Dissolution Test:

The release rate of desloratadine from the fast dissolving tablet is determined using dissolution testing apparatus type -1(paddle method). The dissolution test is performed using 900ml of 0.1N HCL, at 37 $\pm$0.5℃and 50 rpm.A sample (5ml) of the solution is withdrawn from the dissolution apparatus at 5,10,15,20,25,30 min.The samples are replaced with fresh dissolution medium of same quantity.The absorbance of these solutions is measured at 242 nm in UV-Spectrophotometer(Parmar R.B *et al*., 2009).

CHAPTER-X

RESULTS AND DISCUSSION

I. CALIBRATION OF DESLORATADINE IN pH 5.8

The λ_{max} of desloratadine was determined by scanning the 10µg/ml solution of the drug in buffer solution of pH 5.8 using UV-Spectrophotometer and was found to be 242nm. A standard calibration curve for the drug was obtained by measuring absorbance at 242 nm and by plotting the graph of absorbance Vs concentration. The calibration plots of desloratadine were shown in Table-1and Figure-1. The linear correlation co-efficient was found to be $\gamma = 0.9997$. Desloratadine obeys Beer's law within the concentration range of 2-20 µg/ml.

II. CALIBRATION OF DESLORATADINE IN 0.1N HYDROCHLORIC ACID

The λ_{max} of desloratadine was determined by scanning the 10µg/ml solution of the drug in buffer solution of 0.1N Hydrochloric acid using UV-Spectrophotometer and was found to be 242 nm. A standard calibration curve for the drug was obtained by measuring absorbance at 242 nm and by plotting the graph of absorbance Vs concentration. The calibration plots of desloratadine were shown in Table- 2 and Figure- 2. The linear correlation co-efficient was found to be $\gamma = 0.9996$. Desloratadine obeys Beer's law within the concentration range of 2-20 µg/ml.

III. PREPARATION OF DRUG RESIN COMPLEX (DRC)

The DRC was prepared with two different resins viz Indion-204 and Indion-234. From the trial, it was found that the Indion-234 resin had maximum percentage drug

bound to resin. And so, Indion-234 was selected for the preparation of drug resin complex. The results were shown in Table-3&4. (Venkada Ramana Retty.S *et al*., 2010)

IV. SELETION OF ION EXCHANGE RESIN (IER)

From the trial, the complex which had maximum quantity of drug loading was selected for further studies. It was found that the maximum percentage drug bound to resin for the Indion-204 is 65.53 ± 2.54 % at the ratio of 1:5 and 88.19 ± 0.68 % of drug bound to resin for Indion-234 at the ratio of 1:5. And so, Indion-234 was selected as the best resin for formulating drug-resin complex. The results were shown in Table-3&4 (Venkata Ramana Retty**.**S *et al*., 2010)

V. EVALUATION OF DRUG RESIN COMPLEX

a) Fourier Transform-Infra Red (FT-IR)Studies:

The Fourier Transform Infra Red Spectroscopy studies were carried out for pure drug, resin, physical mixture of drug-resin and drug-resin complex. The spectra were shown in Figure-3.The spectral analysis of pure drug showed the characteristics peaks at 3423.76cm-^{1} , 3325.39cm-^{1}, 1327.07cm-^{1}, 1292.35cm-^{1}, 844.85 cm-^{1}, 773.48 cm^{-1}. All the above characteristic peaks appear in the spectra of all samples were within the same wavelength number. This indicates that there were no interactions between the drug and resin.

b) Differential Scanning Colorimetric (DSC) Studies:

The DSC thermograms of pure drug, resin, drug-resin complex were shown in the Figure-4. An endothermic peak corresponding to the melting point of pure drug was

prominent in the drug-resin complex which suggested clearly that there was no interaction between drug, resin and drug-resin complex

VI. FORMULATION OF FAST DISSOLVING TABLET OF DESLORATADINE

The fast dissolving tablet of Desloratadine was prepared by direct compression method using different ratio (1.5%, 3%, 4.5%, 6%, and 7.5%) of superdisintegrants (Sodium starch glycolate, Crospovidone and Croscarmellose sodium).The composition of the different formulation were given in Table-5.

Fifteen formulations (F1-F15) were prepared. All the tablets were light pink colour and round in shape having 8 mm diameter.

VII. PRECOMPRESSION EVALUATION FOR POWDER BLEND

i. Angle of Repose:

The angle of repose was used to determine the flow properties of powder blend. The angle of repose of all the formulations ranged from 28˚.35' to 31˚.79'. The results indicated that all the formulations exhibited good flow properties. The results of angle of repose for all the formulations were shown in Table-6.

ii. Bulk density:

The bulk density was used to determine the free flowing properties of powder blend. The bulk density of all the formulations was in the range of 0.47 - 0.52 g/cm$^{3.}$ The values of bulk density showed that the blend was not tightly packed and indicated good flow properties. The results of bulk density for all the formulations were shown in Table-6.

iii. Tapped Density:

The tapped density was used to access the free flowing properties of powder blend. Table tapped density of all the formulations were in the range of 0.52 - 0.59 g/cm^3. The results indicated that the blends of all the formulation had good flow properties. The results of tapped density for all the formulations were shown in Table-6.

iv. *Carr's Compressibility Index*:

The carr's compressibility index was used to access the free flowing properties of powder blend..The compressibility index of all the formulations ranged from 9.98 - 15.78 %. This value below 15% indicates a powder having good flow property and good propensity of compression. The results of compressibility for all formulations were shown in Table-6.

v. Hausner's Ratio:

The Hausner's ratio was an indirect index of ease of powder flow. The Hausner's ratio of all the formulations ranged from 1.11-1.18. It was less than 1.25 indicated better flow property of blend. The results of Hausner's ratio for all the formulations were shown in Table-6.

vi. *Drug Content:*

The drug content of the tablets was used to ensure the therapeutic dosage of the active ingredient in the formulation. The drug content of all the formulation was in the range of 97.04 – 101.49%. The results indicated all the formulations were within the acceptable limits as per USP. The results were shown in Table-6.

VIII. POST COMPRESSION EVALUATION

The prepared tablets were evaluated on various parameters such as thickness and diameter, hardness, weight variation, friability, uniformity content, wetting time, water absorption ratio, *In-vitro* disintegration time and *In-vitro* dissolution test. The results were summarized in Table-7.

i. Thickness and Diameter:

The thickness and diameter of all the formulations were used to determine the uniformity of size and shape of the tablets. From the results it was found that the thickness of the tablet in all formulation was 3mm and the diameter of the tablet in all formulation was 8mm.The results indicating all the formulations had uniform size and shape. The results were shown in Table-7.

ii. Hardness:

The hardness of the tablets was used to determine the resistance capacity of the tablets to chipping, abrasion or breakage under conditions of storage, transportation and handling before usage. The hardness of the tablets of all the formulations was found to be 3kg/cm^2. The result indicated that all the tablets had a good mechanical strength. The results of the hardness for all the formulations were shown in Table-7.

iii. Weight Variation Test:

The weight variation test was used to ensure the uniformity of the tablet in all formulations. The weight of all the tablets from each formulation was in the range from 178.52 - 207.46 mg to 204.12 - 237.2 mg. It was found all the tablets passed weight

variation test, as the percentage weight variation was within the acceptable limits of 7.5%. The results were shown in Table-7.

iv. Friability:

Friability test was measured to ensure the mechanical strength of tablet. The results showed that the friability of all the formulation was ranged from 0.36 % to 0.9 %. Friability of all the formulation was lesser than 1 % which indicated the tablets had a good mechanical resistance. The results were shown in Table-7.

v. Uniformity of Content:

The uniformity content test was used to determine the uniform amount of active ingredient present in all formulations. The drug content in the content uniformity of all the formulations was found to be in the range of 95.56 % - 101.23 %. The results indicated all the formulations were within the acceptable limits as per USP limits. The results were shown in Table-7.

vi. Wetting Time:

Wetting time of the tablet was used to assess the capacity of the tablets to disintegrate by swelling of water. All the formulations showed quick wetting, this may be due to ability of swelling and also capacity of absorption of water. The results of wetting time of all the formulations were shown in Table-7.

The formulations F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, F12, F13, F14, F15 showed the wetting time 47, 56, 40, 35, 27, 26, 14, 8, 8, 5, 17, 16, 17, 14, 11 seconds respectively. The results indicated that as the concentration of superdisintegrant

increased wetting time was decreased. Formulation F10 containing Crospovidone (7.5%) shows lesser wetting time than other formulation.

This may be due to fact that Crospovidone and Croscarmellose sodium perform their disintegrating action by wicking through capillary action and fibrous structure respectively with minimum gelling.Sodium starch glycolate is disintegrated by swelling mechanism leading to longer wetting time. (N.G.Raghavendra Rao *et al*., 2010)

.***Water Absorption Ratio:***

The water absorption ratio test was used to ensure the capacity of the superdisintegrant to absorb the water. The results of water absorption ratio of all the formulation were shown in Table-7.

Formulations F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, F12, F13, F14, F15 showed the water absorption ratio 55.26%,59.07%,68.60%,75.13%, 86.27%, 63.91%, 72.82%, 80.71% 88.27%, 91.71%, 69.97%, 77.65% 78.17%, 82.05%, 83.92% The results showed that,as concentration of superdisintegrant increased water absorption ratio was also increased. Formulation F10 containing Crospovidone shows highest water absorption ratio (91.71%) than other formulation.

The reason for high water absorption ratio for Crospovidone may be due to highly porous structure, it draws large amount of water by water wicking mechanism into porous network of tablet resulting rapidly absorbs water into its network, and highest than formulation prepared with other superdisintegrants. It was indicated that water absorption ratio increased with decrease in wetting time. (Arvind S.Singh *et al*., 2010)

vii. In-Vitro Disintegration Time:

The *In- vitro* disintegration time was determined by disintegration test apparatus. Formulations F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, F12, F13, F14, F15 showed the disintegration time 48, 47, 44, 30, 20, 23, 16, 10, 8, 6, 15, 13, 14, 11, 10 seconds respectively. It was observed that Formulation F10 containing Crospovidone (7.5%) containing tablet disintegrate rapidly in a short time (6 seconds).The results of disintegration of all the tablets were found to be lesser than1 min and so satisfied the criteria of fast dissolving tablets. The results were shown in Table-7.

The faster disintegration time of Crospovidone tablets may be attributed to its rapid capillary activity and pronounced hydration with little tendency to gel formation. Thus these results suggest that the disintegration times can be decreased by using wicking type of disintegrants (Ajay Kumar Patil *et al*., 2011).

viii. In-vitro Dissolution Studies:

The results of *In-vitro* drug release studies from fast dissolving tablets of desloratadine were shown in the Table-7 .Figure5, 6, 7, and 8.

The results showed that the release profiles of different formulations varied according to the type of superdisintegrants and its percentage to the formulations. Maximum percentage of drug (More than 90%) was released from the all formulations within 10 minutes.

***Effect of Superdisintegrant on Drug Release**:*

The formulations F1, F2, F3, F4, F5 were prepared with 1.5% , 3% , 4.5% , 6% , 7.5% Sodium starch glycolate as a superdisintegrant, showed the cumulative percentage of drug release 95.82%, 95.75%, 96.42%, 91.83%, 92.19% respectively at 10 minutes. Formulation F3 containing 4.5% Sodium starch glycolate shows maximum drug release (96.42 %,) at 10 minutes. This result indicated that the optimum concentration of Sodium starch glycolate was 4.5%.

The formulation F6, F7, F8, F9, F10 were prepared with 1.5% , 3% , 4.5% , 6% , 7.5% Crospovidone as a superdisintegrant, showed the cumulative percentage of drug release 96.68% , 94.54% , 93.48% , 96.55% , 97.12% respectively at 10 minutes.Formulation F10 containing 7.5% Crospovidone shows maximum drug release (97.12 %,) at 10 minutes. This result indicated that the optimum concentration of Crospovidonewas 7.5%

The formulation F11, F12, F13, F14, F15 were prepared with 1.5% , 3% , 4.5% , 6% , 7.5% Croscarmellose sodium as a superdisintegrant, showed the cumulative percentage of drug release 90.95% , 91.55% , 93.43% , 95.09% , 93.71% respectively at 10 minutes .Formulation F14 containing 6% Croscarmellose sodium shows maximum drug release (95.09 %,) at 10 minutes. This result indicated that the optimum concentration of Croscarmellose Sodium was 6%.

From the results, the release rates of superdisintegrants were in the order:

Crospovidone > Sodium starch glycolate > Croscarmellose sodium

The maximum percentage of drug release was achieved by the formulation containing Crospovidone (7.5%) as a superdisintegrant. It may be due to the results in the rapid disintegration of tablet in dissolution medium resulting in maximum drug release. Among fifteen formulations, formulation 10 (F-10) was selected as a best formulation because of its lowest disintegration time and highest drug release.(C.P.Jain *et al*., 2009)

TABLE: 1 CALIBRATION OF DESLORATADINE IN pH 5.8

S.No	Concentration in µgm/ml	Absorbance (Avg ± SD)
1	2	0.081 ± 0.0021
2	4	0.144 ± 0.0018
3	6	0.233 ± 0.0026
4	8	0.317 ± 0.0016
5	10	0.406 ± 0.0038
6	12	0.482 ± 0.0041
7	14	0.573 ± 0.0054
8	16	0.660 ± 0.0024
9	18	0.741 ± 0.0012
10	20	0.823 ± 0.0047
		R^2 0.9997

TABLE 2: CALIBRATION OF DESLORATADINE IN 0.1N HYDROCHLORIC ACID

S.No	Concentration in µgm/ml	Absorbance (Avg ± SD)
1	2	0.060 ± 0.0009
2	4	0.152 ± 0.0008
3	6	0.239 ± 0.0006
4	8	0.323 ± 0.0012
5	10	0.397 ± 0.0012
6	12	0.488 ± 0.0008
7	14	0.562 ± 0.0008
8	16	0.643 ± 0.0012
9	18	0.728 ± 0.0004
10	20	0.798 ± 0.0004
		R^2 0.9996

TABLE NO: 3 DESLORATADINE-INDION 204 DRUG-RESINS COMPLEX

S.NO	DRUG-RESIN RATIO	% OF DRUG BOUND TO RESIN (Average ± S.D)
1	1:1	58.93 ± 1.66
2	1:2	64.89 ± 1.18
3	1:3	61.31 ± 0.32
4	1:4	65.53 ± 2.54
5	1:5	61.59 ± 3.34

TABLE NO; 4 DESLORATADINE-INDION 234 DRUG RESIN COMPLEX

S.NO	DRUG-RESIN RATIO	% OF DRUG BOUND TO RESIN (Average ± S.D)
1	1:1	76.66 ± 0.68
2	1:2	74.11 ± 0.73
3	1:3	85.25 ± .049
4	1:4	85.96 ± 1.17
5	1:5	88.19 ± 0.68

TABLE NO; 5 FORMULATION OF FAST DISSOLVING TABLET OF DESLORATADINE

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
DRC (Eq.to 5mg of desloratadine) (mg)	34.45	34.45	34.45	34.45	34.45	34.45	34.45	34.45	34.45	34.45	34.45	34.45	34.45	34.45	34.45
Sodium starchglycolate(mg)	3	6	9	12	15	–	–	–	–	–	–	–	–	–	–
Crospovidone (mg)	–	–	–	–	–	3	6	9	12	15	–	–	–	–	–
Croscarmellose sodium(mg)	–	–	–	–	–	–	–	–	–	–	3	6	9	12	15
Mannitol (mg)	55	55	55	55	55	55	55	55	55	55	55	55	55	55	55
Microcrystalline cellulose(mg)	99.55	96.55	93.55	90.55	87.55	99.55	96.55	93.55	90.55	87.55	99.55	96.55	93.55	90.55	87.55
Sodium saccharin (mg)	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Peppermint flavor (mg)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium stearate (mg)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Talc (mg)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Total Weight (mg)	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200

TABLE NO; 6 EVALUATION OF MIXED BLEND OF DRC AND EXCIPIENTS

Formulation	Angle of repose(°)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility index (%)	Hausner's ratio	Drug content (%)
F1	31.79	0.50	0.59	15.78	1.1874	97.78
F2	30.27	0.52	0.59	11.10	1.1249	101.23
F3	30.80	0.49	0.53	10.54	1.1177	97.78
F4	29.91	0.47	0.52	9.98	1.1109	100.49
F5	29.49	0.50	0.56	10.54	1.1178	98.27
F6	29.74	0.50	0.56	10.53	1.1176	98.52
F7	29.92	0.50	0.55	10.53	1.1177	97.04
F8	29.07	0.49	0.55	10.54	1.1178	97.78
F9	29.51	0.47	0.52	10	1.1111	99.01
F10	29.55	0.49	0.55	10.52	1.1175	96.79
F11	29.25	0.50	0.55	10.52	1.1176	99.26
F12	29.49	0.49	0.56	10.53	1.1176	98.76
F13	28.35	0.49	0.55	10.48	1.1170	97.04
F14	28.84	0.49	0.55	10.52	1.1176	98.52
F15	28.72	0.49	0.56	10.53	1.1176	99.01

TABLE NO; 7 EVALUATION OF FAST DISSOLVING TABLETS

Formulation code	Thickness (mm)	Diameter (mm)	Hardness (Kg/cm^2)	Weight variation range(mg)	Friability (%)	Water absorption ratio (%)	Wetting time (sec)	Content uniformity (%)	Disintegration time (sec)	Max % of drug release at 10 min (Avg ± S.D)
F1	3	8	3	202.08-234.84	0.79	55.26	47	97.78	48	95.82 ± 0.67
F2	3	8	3	200.84-233.4	0.88	59.07	56	101.23	47	95.75 ± 1.095
F3	3	8	3	191.9-223	0.63	68.60	40	97.78	44	96.42± 0.538
F4	3	8	3	204.12-237.2	0.69	75.13	35	100.49	30	91.83 ± 0.66
F5	3	8	3	179.24-208.3	0.36	86.27	27	98.27	20	92.19 ± 0.844
F6	3	8	3	182.04-211.56	0.67	63.91	26	97.53	23	96.68 ± 0.658
F7	3	8	3	182.93-212.59	0.38	72.83	14	96.55	16	94.54 ± 0.586
F8	3	8	3	178.78-207.76	0.47	80.71	8	96.79	10	93.48 ± 0.588
F9	3	8	3	179.92-209.08	0.71	88.27	8	95.56	8	96.55 ± 0.528
F10	3	8	3	185.72-215.82	0.58	91.71	5	96.05	6	97.12 ± 0.374
F11	3	8	3	178.52-207.46	0.57	69.97	17	97.78	15	90.95 ± 0.374
F12	3	8	3	183.12-212.8	0.87	77.65	16	98.02	13	91.55 ± 0.769
F13	3	8	3	184.13-213.97	0.9	78.17	17	96.55	14	93.43 ± 0.597
F14	3	8	3	184.51-214.43	0.83	82.05	14	98.27	11	95.09 ± 0.757
F15	3	8	3	182.97-212.63	0.72	83.92	11	97.78	10	93.71 ± 0.527

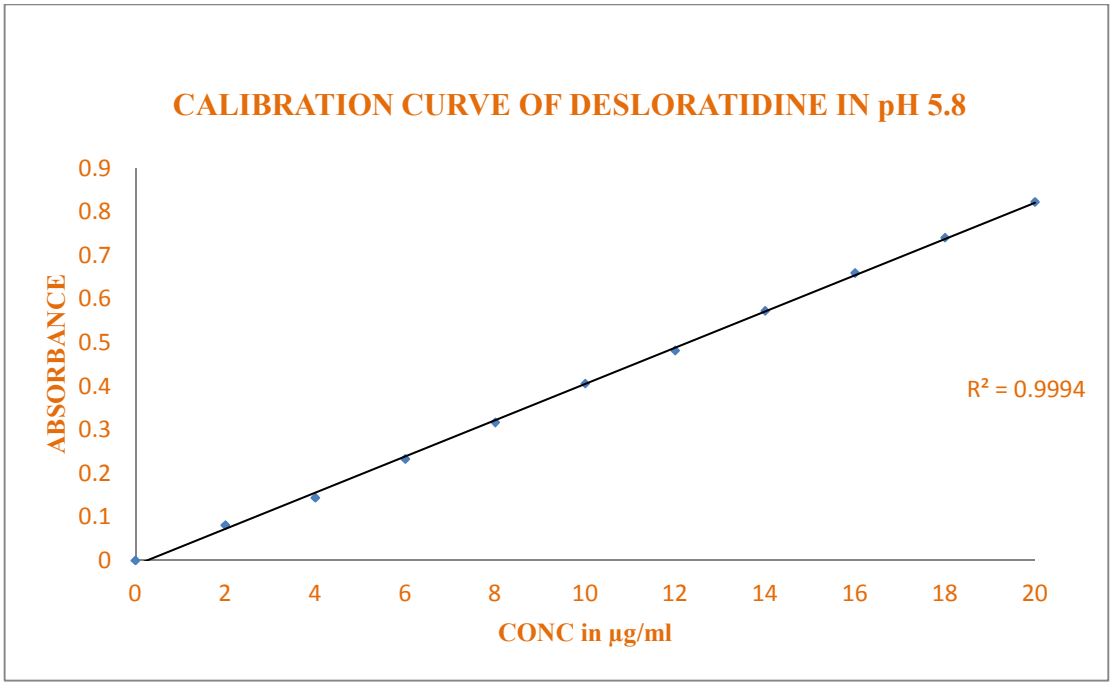

CALIBRATION CURVE OF DESLORATIDINE IN pH 5.8
ABSORBANCE
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2
4
6
8
10
12
14
16
18
20
CONC in µg/ml
R² = 0.9994

FIGURE: 1

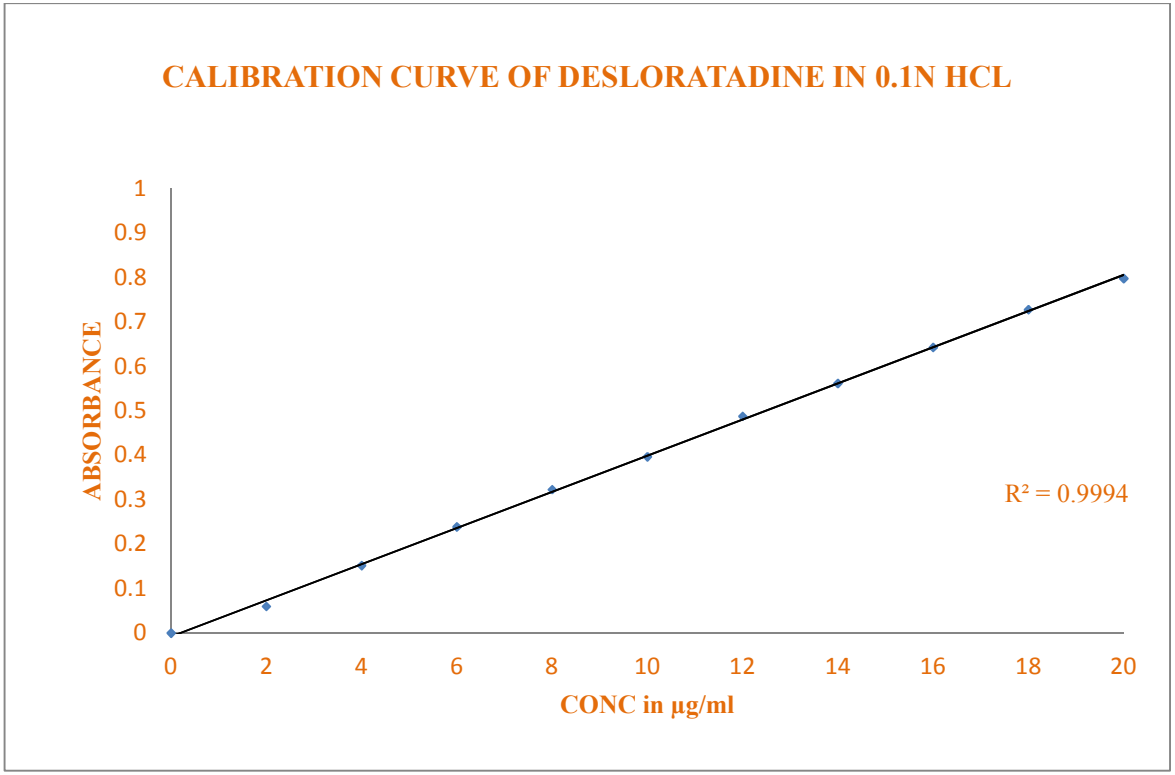

CALIBRATION CURVE OF DESLORATADINE IN 0.1N HCL
ABSORBANCE
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2
4
6
8
10
12
14
16
18
20
CONC in µg/ml
R² = 0.9994

FIGURE: 2

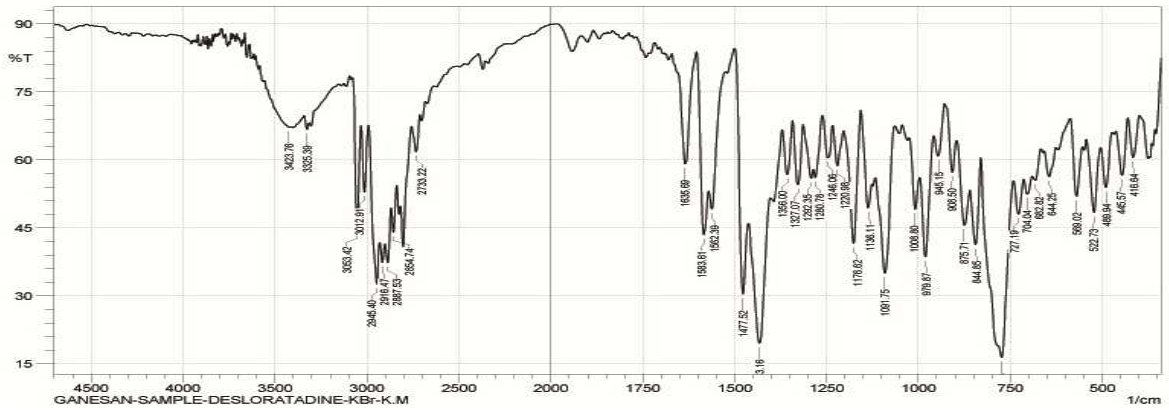
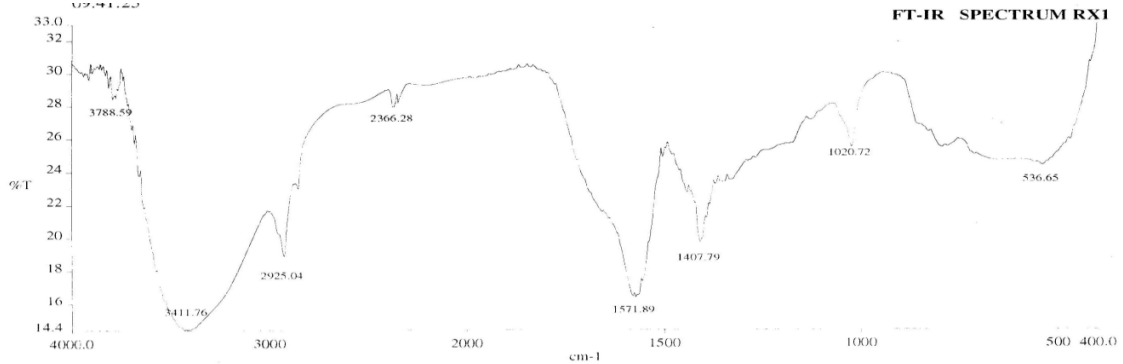
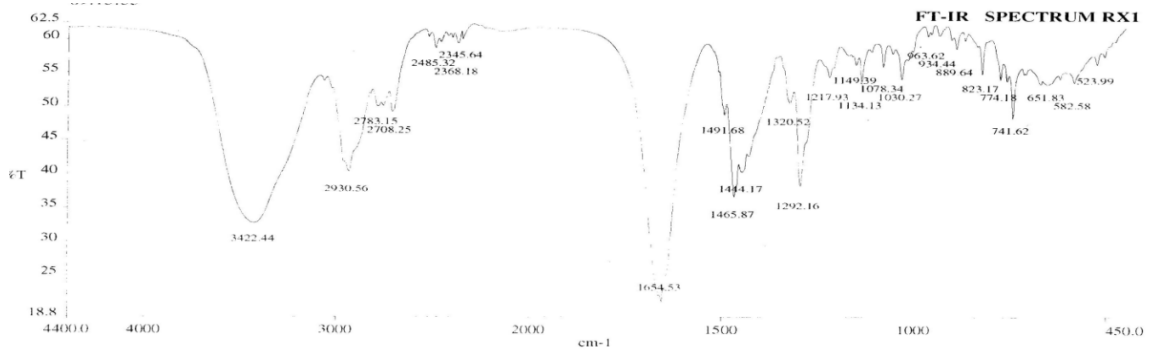


FIG 3 FTIR SPECTRA DRUG



INDION 234


FT-IR SPECTRUM RX1
%T
cm-1
62.5
60
55
50
45
40
35
30
25
18.8
4400.0
4000
3000
2000
1500
1000
450.0
3422.44
2930.56
2783.15
2708.25
2485.32
2345.64
2368.18
1654.53
1491.68
1465.87
1464.17
1320.52
1292.16
1217.93
1134.13
1149.39
1078.34
1030.27
963.62
934.44
889.64
823.17
774.18
741.62
651.83
582.58
523.99

DRC

DSC THERMOGRAMS

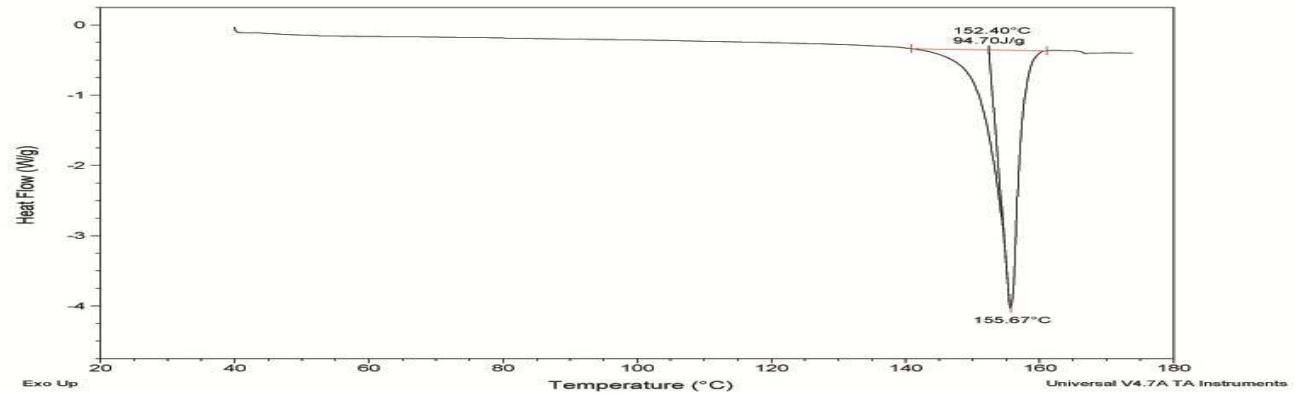
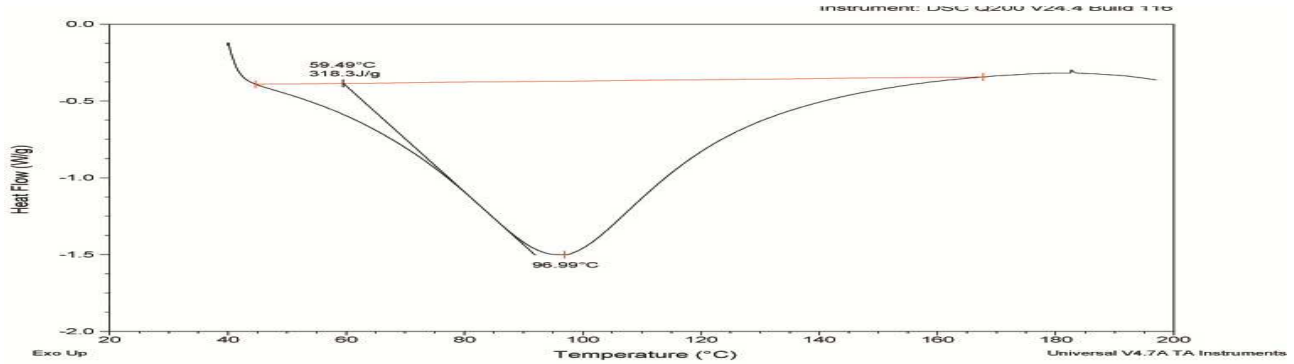
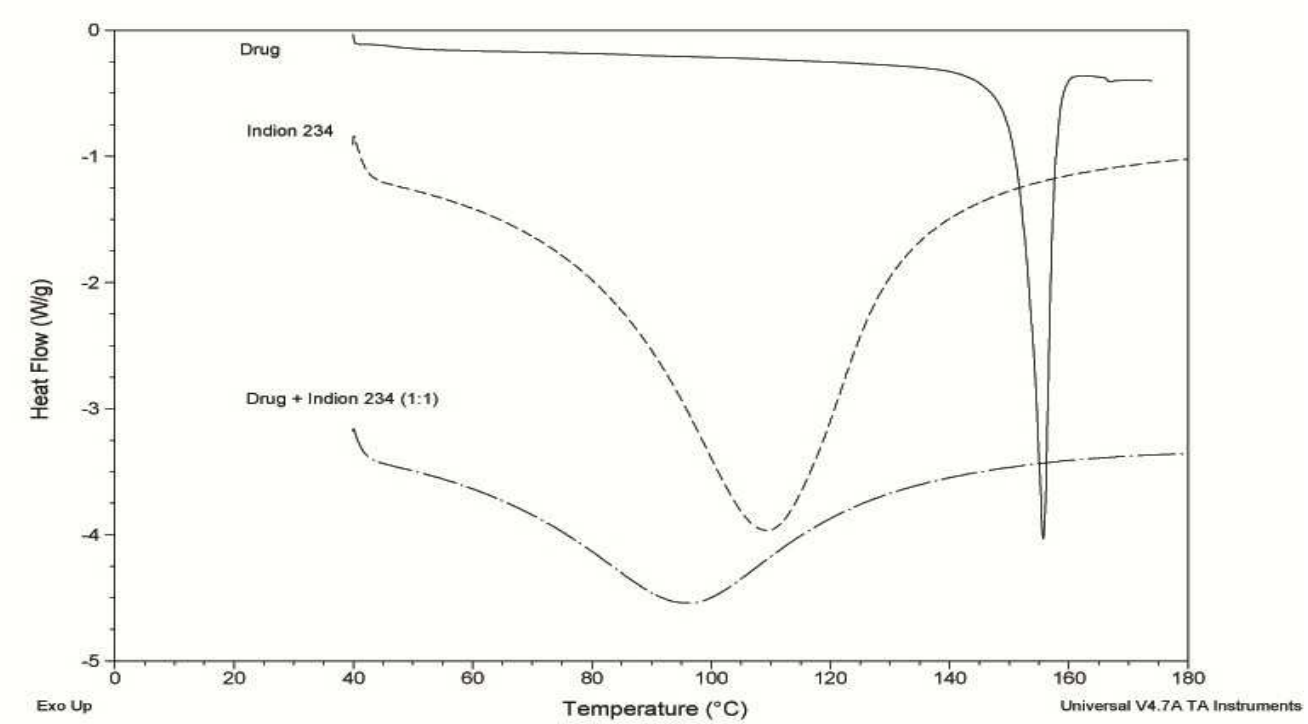


FIGURE 4 DRUG



INDION 234


Drug
Indion 234
Drug + Indion 234 (1:1)
Heat Flow (W/g)
Temperature (°C)
Exo Up
Universal V4.7A TA Instruments
0
-1
-2
-3
-4
-5
0
20
40
60
80
100
120
140
160
180

DRC

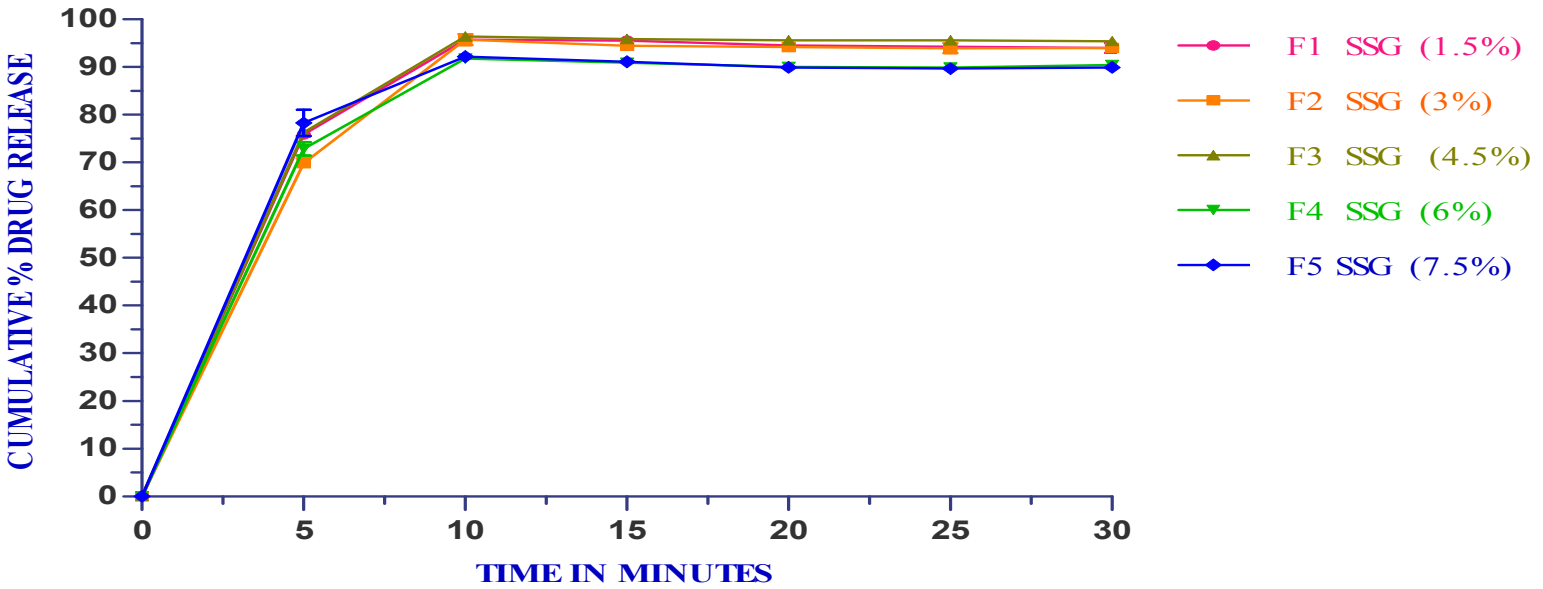


FIG 5

COMPARISON OF INVITRO RELEASE PROFILE OF DESLORATADINE CONTAINING DIFFERENT PERCENTAGE OF SODIUM STARCH GLYCOLATE

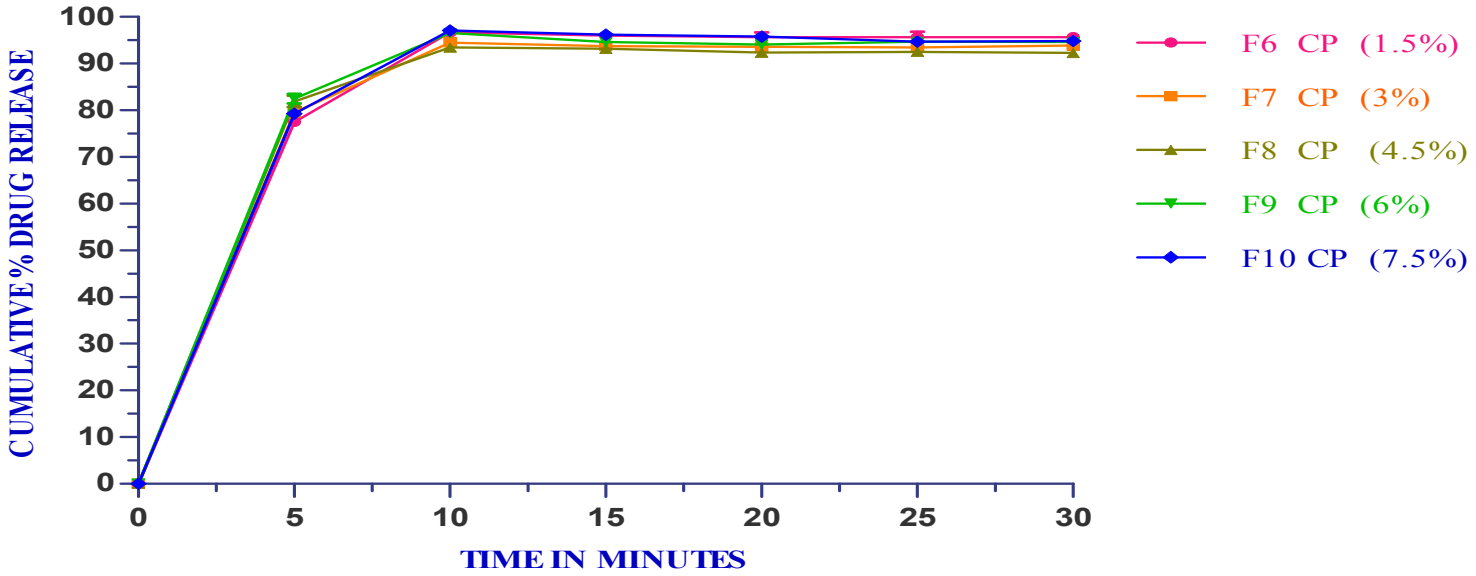


FIG 6

COMPARISON OF INVITRO RELEASE PROFILE OF DESLORATADINE CONTAINING DIFFERENT PERCENTAGE OF CROSPOVIDONE

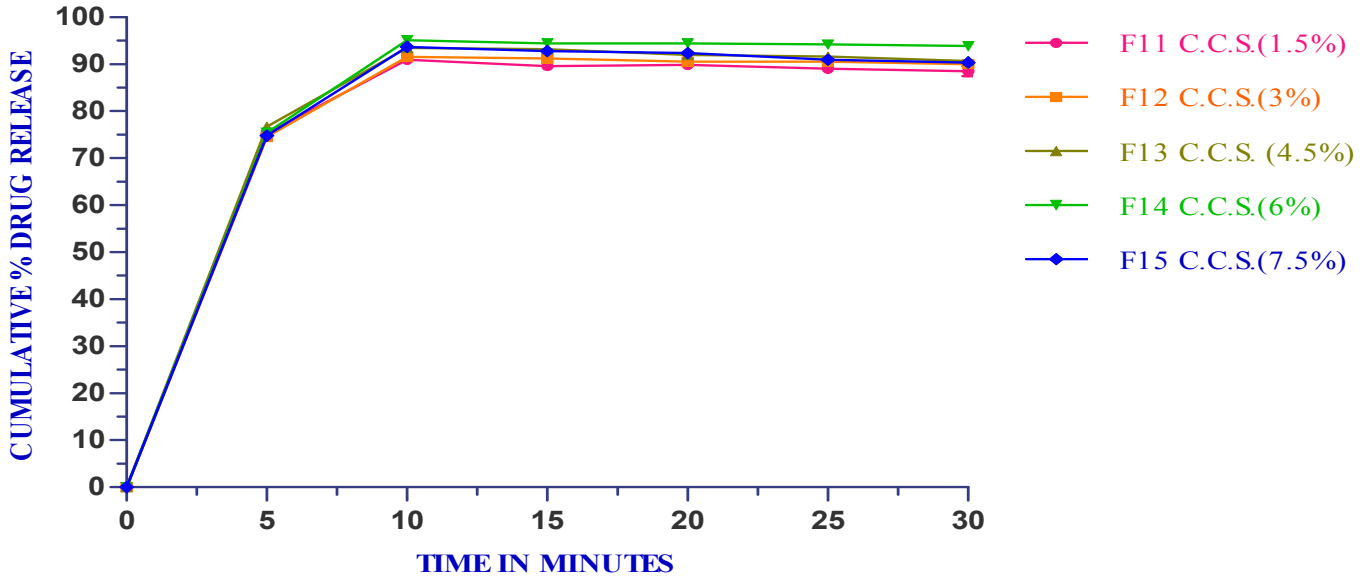


FIG 7

COMPARISON OF INVITRO RELEASE PROFILE OF DESLORATADINE CONTAINING DIFFERENT PERCENTAGE OF CROSCARMELLOSE SODIUM

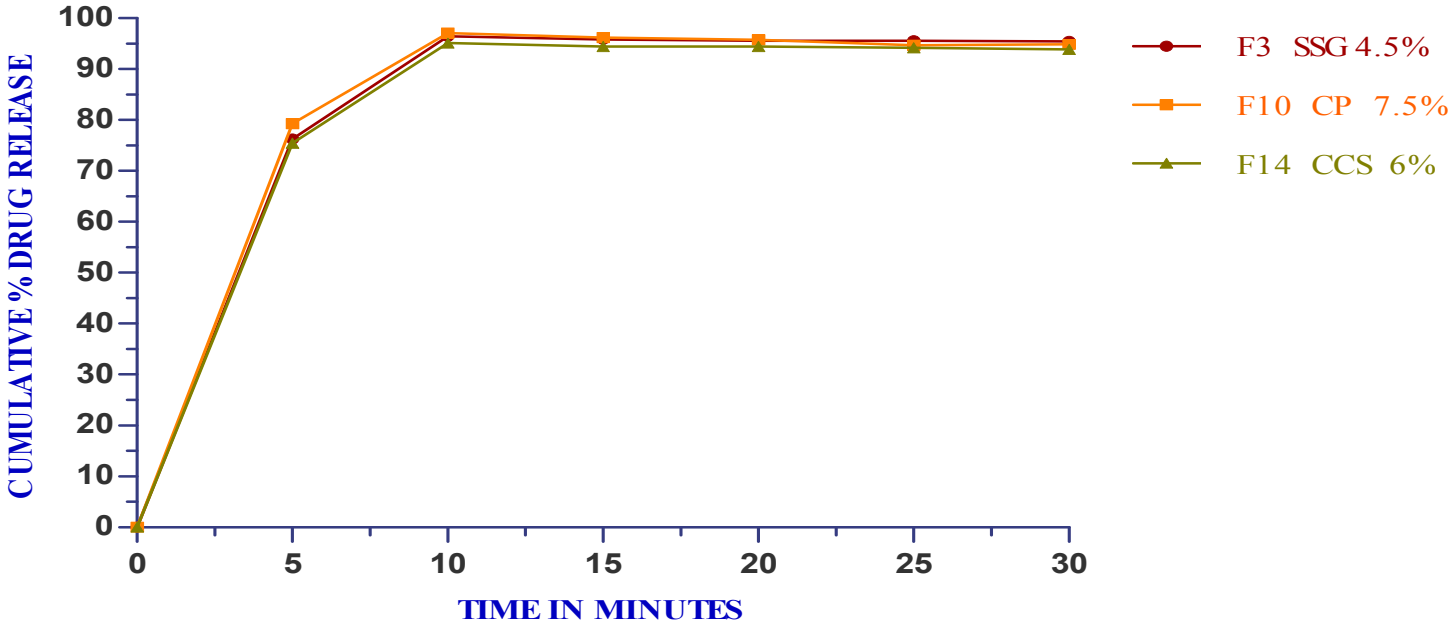


FIG 8

COMPARISON OF INVITRO RELEASE PROFILE OF DESLORATADINE CONTAINING DIFFERENT SUPER DISINTEGRANTS

CHAPTER-XI

SUMMARY AND CONCLUSION

Desloratadine is a selective, H1 receptor antihistamine drug having bitter in taste. It is the major orally active metabolite of loratadine, approved for allergic rhinitis and/or chronic idiopathic urticaria. Problems like hand tremors, dysphasia and non-co-operative patients, the problems of swallowing is a common phenomenon which leads to poor patient compliance and ineffective therapy.

Fast dissolving tablets are gaining prominence as a new drug delivery system, which disintegrate or dissolve in the oral cavity within a minute without the need of water or chewing. In the present study, an attempt has been made to prepare bitterless fast dissolving of desloratadine with good mouth feel so as to prepare a "patient-friendly dosage form".

The drug is dispersed in purified water under stirring at 100rpm in room temperature. The ph of the drug dispersion is adjusted to PH 6.5± 0.5 with 2% citric acid solution. The resin is then added to the ph adjusted drug dispersion and stirred for 3 hours. The dispersion is filtered through whatman filter paper NO; 41.

The DRC is formed with two resins (INDION-204, INDION-234). In each case 100mg of drug in deionised water is stirred with resin containing various drug-resin ratio (1:1, 1:2, 1:3, 1:4, 1;5) by using magnetic stirrer. Then the dispersion is filtered through whatman filter paper NO; 41.The amount of drug loaded is determined indirectly by estimating the amount remaining to be loaded in solution spectrometrically at 242 nm in UV-Spectrophotometer. The resin to which the drug bound to maximum percentage is selected for further studies.

An accurately weighed quantity of DRC is mixed with different ratio (1.5%, 3%, 4.5%, 6% and 7.5%) of superdisintegrants (CCS, CP, SSG).The drug resin complex along with MCC, Mannitol, Saccharin sodium and Peppermint flavor in geometrical dilution. Then Magnesium stearate and Talc were added, mixed and compressed into tablets using single punch tablet punching machine.

Disintegration time is measured in 900ml of artificial Saliva (PH 5.8) at 37± 0.5℃.The disintegration time of 3 tablets are recorded and the average is reported.

Dissolution test is determined by USP dissolution testing apparatus type-2(paddle method). It is performed using 900ml of 0.1N Hydrochloric acid at 37± 0.5℃ and 50 rpm. A 5ml sample solution is withdrawn from the dissolution apparatus at 5, 10, 15, 20, 25 and 30 minutes. The samples are replaced with fresh dissolution medium of same quantity. The absorbance of the solution is measured at 242 nm in UV-Spectrophotometer.

Indion-234 resin was selected for the preparation of DRC (1:5). The maximum drug loading found to be 88.19±0.68%. The disintegration time of the tablets decreased with increase in concentration of superdisintegrants. The faster disintegration effect of crospovidone tablets may be attributed to its rapid capillary activity and pronounced hydrating with little tendency to gel formation. The fast dissolving tablet formulations were subjected to precompression and post compression parameter and the results were found to be within the acceptable limits. *In vitro* dissolution studies of the all formulation showed more than 90% drug release within 10 minutes. The maximum increase in the dissolution rate was observed with 7.5% Crospovidone (F-10) amongst all formulation. 97.12± 0.37% release was occurring within 10 minutes.F-10 was

found to be best formulation as this showed less disintegration time and more drug release.

Conclusion:

Use of cation exchange resins offers good method for preparing bitterless desloratadine formulation using drug-resin complex. Fast dissolving tablets of desloratadine can be successfully prepared by direct compression method using selected superdisintegrants in order to improve disintegration/dissolution of the drug in oral cavity and hence better patient compliance and effective therapy.

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